MassMEDIC
Massachusetts Medical Device Industry Council

# Drug Delivery Devices (DDD):

## *Increasing role in patient outcome and future trends*
## *New England's global appeal to foster collaboration*

March 2021

AliraHealth

# Table of Contents

# Abbreviations

- **CBER** Center for Biologics Evaluation And Research
- **CDER** Center for Drug Evaluation And Research
- **CDMO** Contract Development And Manufacturing Organization
- **CDRH** Center for Devices And Radiological Health
- **CE** Conformité Européenne
- **CGM** Continuous Glucose Monitoring
- **CMO** Contract Manufacturing Organization
- **CNS** Central Nervous System
- **DDD** Drug Delivery Devices
- **DDS** Drug Delivery Systems
- **DH** Digital Health
- **DPI** Dry Powder Inhalers
- **DTx** Digital Therapeutics
- **EDDS** Electronic Drug Delivery Systems
- **ENT** Ear, Nose, Throat
- **FDA** Food and Drug Administration (US)
- **HC** Health Care
- **HCP** Health Care Professional
- **HFE** Human Factor Engineering
- **IoMT** Internet of Medical Things
- **IP** Intellectual Property
- **MDI** Metered-Dose Inhalers
- **MDR** Regulation (Eu) 2017/745 On Medical Devices
- **ME** Molecular Entity
- **MF** Master Files
- **NE** New England
- **NME** New Molecular Entity
- **OCP** Office of Combination Products
- **OSD** Ophthalmic Squeeze Dispenser
- **PFS** Pre-Filled Syringes
- **pMDI** Pressurized Metered-Dose Inhalers
- **RoA** Route of Administration
- **RWE** Real-World Evidence
- **SMI** Soft Mist Inhalers

# Introduction

The Drug Delivery Systems (DDS) industry has seen significant evolution over the last decade **as the role of devices and formulations is increasingly reinforced in patient care and outcomes.**

The medical device industry has an opportunity to **enhance the patient experience and drive better outcomes** through increased adoption of **patient-centric approaches**. By giving patients a voice throughout the development lifecycle and pairing those insights with a solid understanding of all stakeholders in the healthcare ecosystem, the industry can broaden their scope from enabling the proper usage of a device to generating evidence of the device's positive impact.

This progress has encouraged industry players, including Drug Delivery Devices (DDD) platform developers, medical device CDMOs and pharmaceuticals CDMOs to **develop new strategies to satisfy and anticipate the dynamic needs of their biopharmaceutical customers.**

**In particular, the role of DDD providers in the Pharma industry has evolved from a transactional supplier to more of a partner in innovation** with participation earlier in the new drug development lifecycle. **This shift has proven valuable to stakeholders across the healthcare ecosystem**, including patients, product providers, HCPs, regulatory authorities, and payors.

With digital health and Internet of Medical Things (IoMT) continuing to amplify DDD, it's time for DDD providers to adapt their business models.

This report investigates the market trends and industry dynamics that are driving the **growth of the Drug Delivery Systems Industry** by analyzing:

- The evolution of **Pharma needs and healthcare macrotrends**
- How **industry player strategies** are responding to changing Pharma needs
- **The DDD competitive landscape** and key players' positioning
- **Transactions** over the last 6 years and **correlation with players' strategies**
- **Digital Health** trends and **opportunities for DDD players**
- **The DDD regulatory landscape** in both the US and EU

**Regional spotlight:** Additionally, the report investigates Massachusetts and New England (NE) as a key region for the DDD industry with its strong pool of talent from local universities, pharmaceutical companies, and relevant adjacent manufacturers.

# Methodology

## Report Goal

Investigate the market trends and industry dynamics driving the **growth of the Drug Delivery Devices (DDD) industry.**

## Perimeter

The DDD industry is defined as **the industry composed of the following players:**

**DDD CMOs and CDMOs**

Defined as integrated players providing contract design (optional) and manufacturing of DDD; they do not retain IP.

**DDD platform developers** (or own-IP DDD providers)

Defined as companies which develop proprietary products platforms customizable by customers.

**Design firms**

**The term *DDD* has been preferred to *Drug Delivery Systems* or *DDS*** to avoid confusion with formulation transport methods such as nanoparticles, sometimes also referred to as DDS.

## Methodology

**Primary Interviews**

Alira Health conducted **over 150 interviews** with Pharma decision makers, DDD players, and CDMOs in the past 2 years, met with **8 CEO and VPs** to prepare this report and ran a **quantitative survey** that will be continually updated.

**Market Analysis**

Analyzed the DDD market and product-related trends by route of administration using **bottom-up and top-down approaches.**

**Transaction Landscape**

Researched the strategic rationales and public valuation metrics that characterize M&A deals and publicly traded companies in the DDD industry.

# Section

# Evolving Pharma needs are impacting the DDD decision-making process

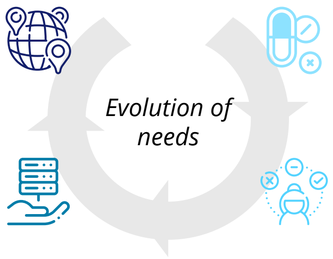
## Executive Summary

***Pharma needs have evolved beyond increasing efficacy and ensuring safety to providing superior patient experience and collecting evidence to support clinical and financial claims. These Pharma considerations are the foundation for DDD decisions.***

### Pharma needs are evolving along the industry

**Monitoring patient adherence and outcome during the drug's commercial phase** to support post-marketing surveillance studies and generate Real-World Evidence (RWE) and Health Economics Outcome Research data.

**Data gathering and adherence monitoring during clinical trials** to enable timely trial-design optimization and improve evidence generation.




**Increase efficacy and ensure safety** of therapy administration, including the appropriate delivery of drugs with specific physiological aspects (e.g. viscosity), to support clinical claims and sustain pricing and reimbursement.

**Improve usability and patient experience**, particularly for patients with condition-related impairments or for self-treatment at-home, to differentiate similar molecules and drive patient compliance.

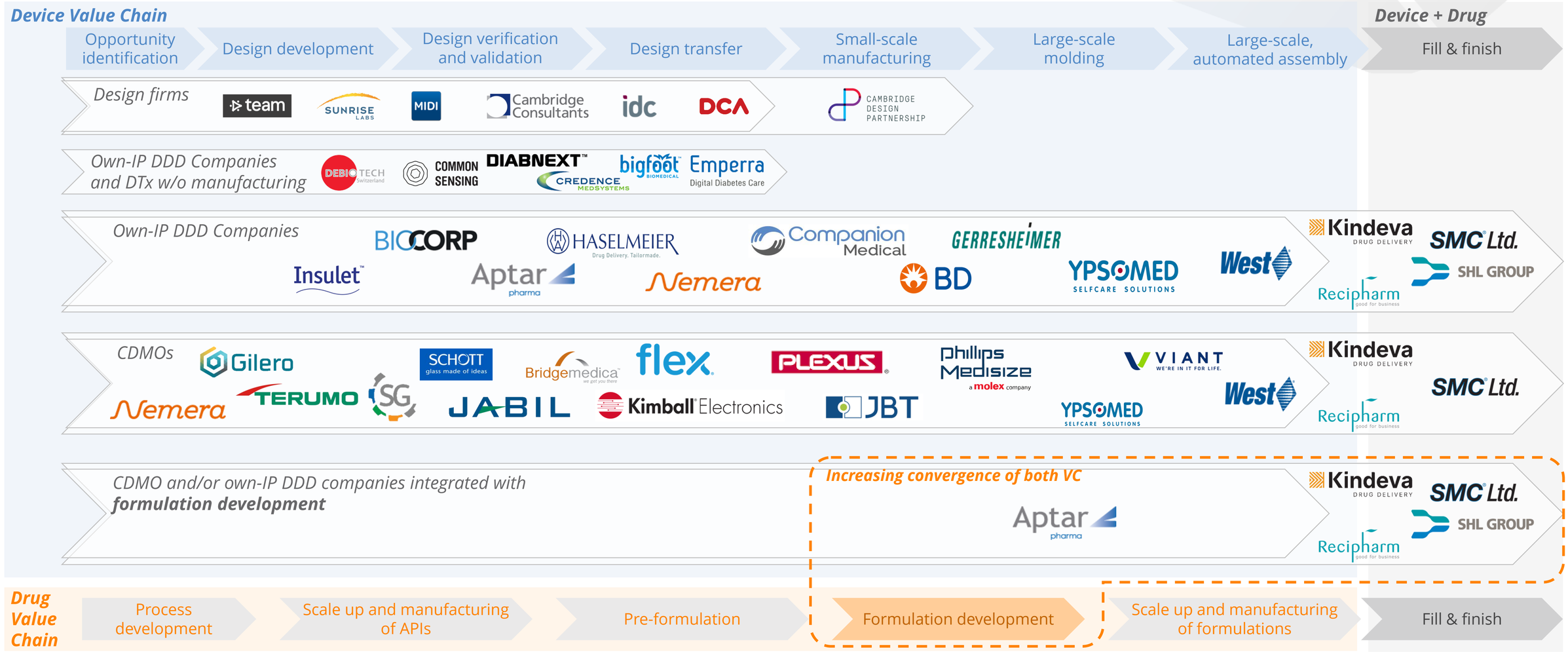
### Key Pharma considerations in the DDD decision-making process

| ***Key consideration*** | **DRUG PHYSIOLOGY** | **PRODUCT DIFFERENTATION AND SETTING OF USE** | **PLATFORM vs. PROPRIETARY DEVICE** | **CONNECTIVITY** |
|---|---|---|---|---|
| ***Rationale*** | Evolving physiology of the drug (viscosity, volume, delivery rate, frequency of use), type of molecule (biologic, small molecule) and end-users (patients, HCP) have been changing DDD's requirements over time. | Needing a DDD in a clinical vs commercial setting impacts DDD requirements and features. | Choosing to develop a proprietary DDD or customizing an existing platform depends on cost, timeline, targeted differentiation and availability of suitable products. | Incorporating connectivity in the DDD is linked to the type of therapy and targeted diseases. Some Pharma may seek differentiation and/or the collection of evidence to support clinical and economic claims. |

Source: Alira Health analysis.

# By creating movement in the DDD industry's value chain

## Executive Summary




Source: Companies public information; Primary interviews; Alira Health analysis.

# And leading to different integration strategies by DDD players

## Executive Summary

***Own-IP DDD players, medical device manufacturers, and pharmaceutical CDMOs are continuously implementing strategies to provide turnkey solutions through the integration of value chain and services.***

### Upstream integration of device-design development services by DDD CDMO players

The addition of design services like conceptualization, user-centric design, and rapid prototyping has allowed DDD CMOs to engage with Pharma clients at earlier stages of the product lifecycle with the objective of converting them to large-volume manufacturing.

*Nemera, a DDD CMO, acquired Insight Product Development, a device-design firm, to strengthen its capabilities in DDD early-stage development and become an integrated CDMO.*


### Integration of early-stage drug development services by device manufacturer (and vice-versa)

To differentiate their offering, provide turnkey solutions, and become partners from the earliest stages, own-IP and CDMO players are increasingly integrating early-stage drug development and formulation services. On the drug development side, pure pharmaceutical CDMOs are eyeing the integration of device capabilities.

*Aptar Pharma, an own-IP DDD provider, acquired Nanopharm, a provider of orally inhaled and nasal drug product-design and -development services, and Gateway Analytical, which provides predictive analytical services for injectable medicines.*

### Acquisition of IP by CMOs and CDMOs

CDMOs have started to develop, acquire, or in-license own-IP platforms to differentiate their offerings, collaborate with clients earlier, integrate the value chain, and capture more margins.

*Sulzer acquired Haselmeier, a Swiss-German own-IP developer and manufacturer of injection drug delivery devices. With this acquisition, Sulzer aims to complement its healthcare portfolio and leverage its expertise in precision injection molding.*

### Prospection of the digital health space

Players are acquiring, hiring, or partnering to add connected solutions to their portfolios. They're developing specific capabilities like electronics, software, cloud architecture, and data analytics to stay competitive in the growing digital health space.

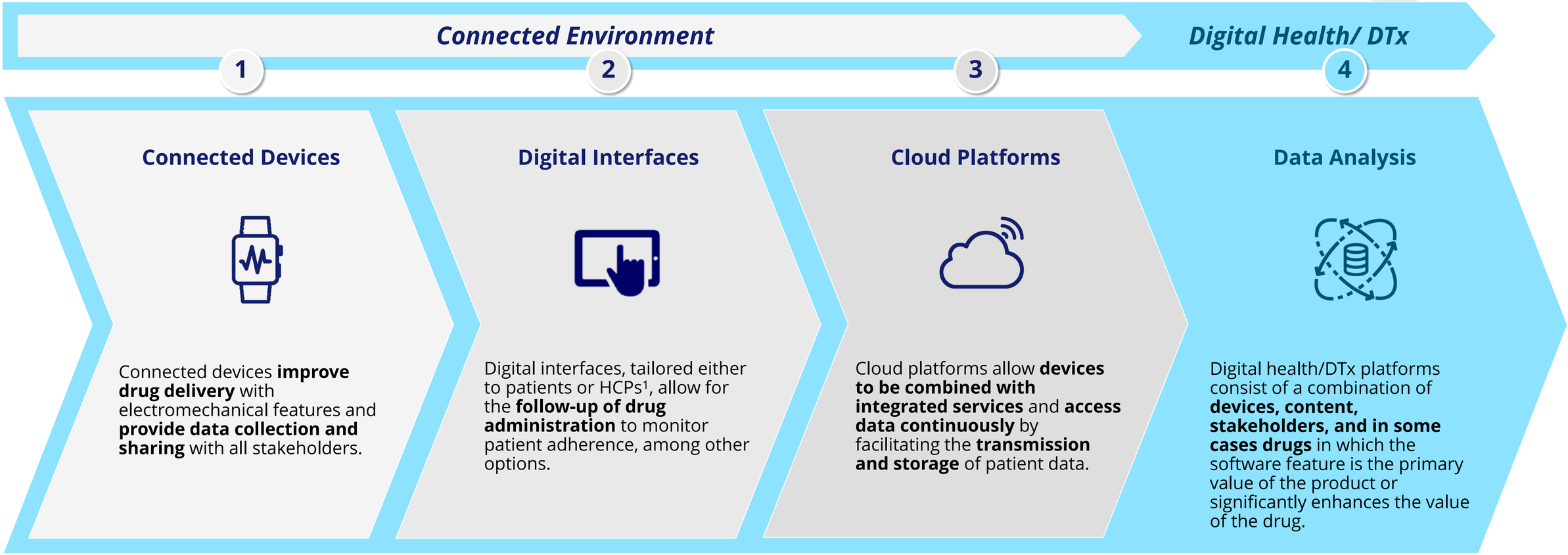
*Aptar Pharma acquired Cohero Health, a respiratory-management digital therapeutics company in 2020.*

Source: Alira Health analysis.

# With increasing consideration of Digital Health

## Executive Summary

***Digital Health solutions and Digital Therapeutics (DTx) encompass connected devices, digital interfaces, and cloud platforms in an ecosystem composed of many stakeholders.***




Note: [1]HCPs: Healthcare Professionals. Source: Alira Health analysis.

# Section

# Drug-delivery devices evolved over time…

## The Evolution of Drug-delivery Devices

***DDDs are used to deliver and/or release medications throughout the body in a controlled and safe way via different routes of administration. Over the years, they have evolved to play a more active role in delivery while increasing drugs' safety and efficacy.***

### Overview, History, and Evolution of Drug-delivery Devices

**DDDs create a vehicle that allows for the proper release, absorption, and distribution of a drug/product at the time of administration and throughout the treatment.**

*Time*

#### First DDD as alternative to oral medicines

During the 17th and 18th centuries, drug-delivery devices were invented as **an alternative to oral administration,** which was then the most convenient method, but was facing barriers such as drugs' poor water solubility or permeability, which made it difficult to develop oral formulations.

#### Development of DDDs as we know them today

**Wave of innovation and development of delivery devices as we know them:** metered-dose inhalers (MDI) and pre-filled syringes (PFS) were developed in the 1950s, autoinjectors in the 1970s, and dry-powder Inhalers in the 1980s, among many others.

However, **such devices are limited to primary and secondary packaging functions** and can create some issues in the safety and efficacy of the treatment delivery, as it **wasn't possible to control the rate, time, and location of drug release.**

#### Increase of drugs' safety and efficacy through DDD

In recent years, the perception of the value of DDDs has been shifting from being a device enabling the delivery of a therapeutic agent to **having an active impact on the drug's performance**. DDDs have gained importance as they **address the main delivery challenges** (i.e., side effects, lack of efficiency, patient usability, etc.) and add value to the drug.

DDDs can now also be connected and included in digital-health ecosystems, gaining an important role in **adherence-monitoring and data-gathering, allowing the demonstration of outcomes sustaining pricing and reimbursement.**

> "DDDs are becoming more and more important and they are no longer just secondary packaging as in the past. Today, for the first time ever, the device is almost on an equal footing with the drug."
>
> *Executive at a global CDMO*

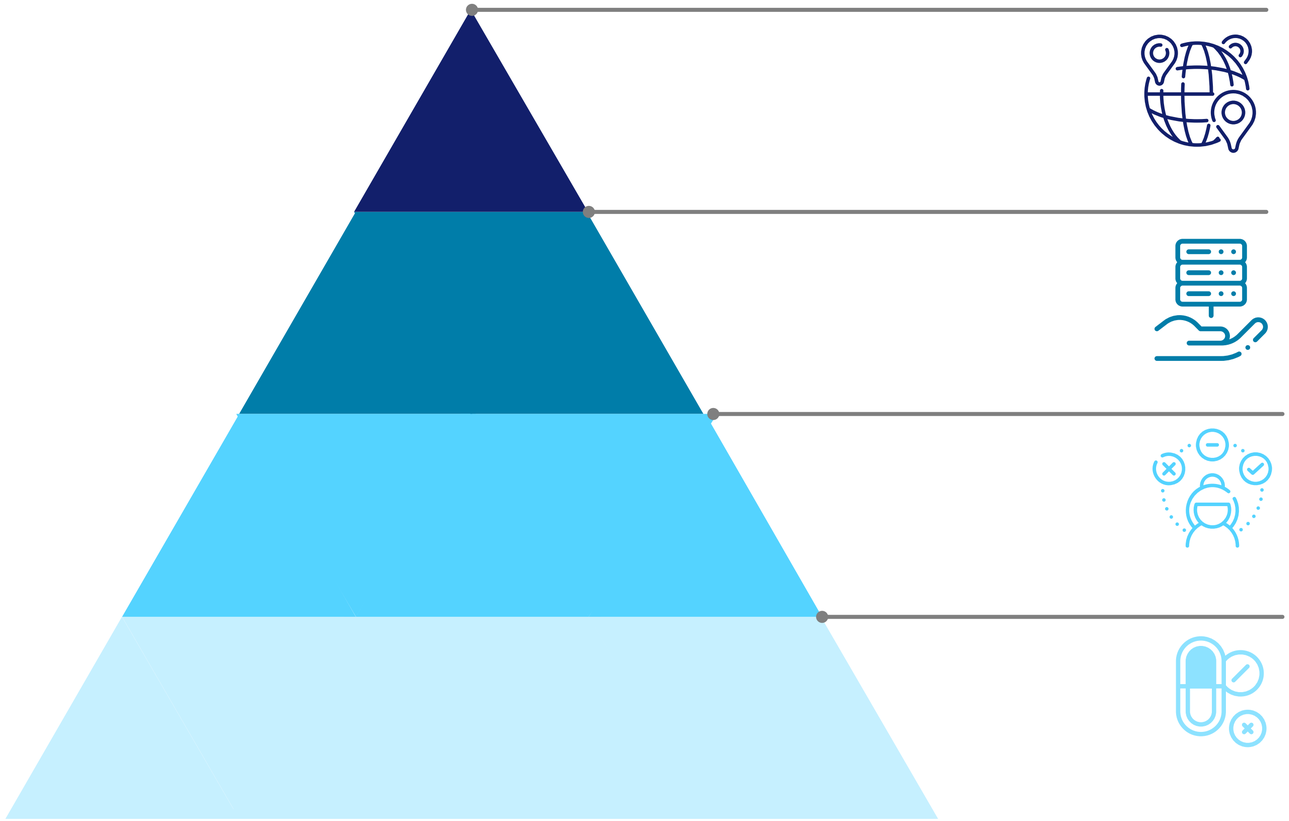
> "Pharmaceutical companies and DDD companies have made huge efforts to provide more patient-friendly and patient-centered devices."
>
> *Executive at a global own-IP DDD company*

Source: *Science Focus*, "The history of medicinal drugs helps explain our relationship with them today," 2019; E.H. Ackerknecht, A Short History of Medicine, 2016; British Society for Immunology, Inhaler (1956); D. Sacha, J.A. Rogers, R.L. Miller, "Pre-filled syringes: a review of the history, manufacturing and challenges", 2015; Primary interviews; Alira Health analysis

# ...to better answer changing pharma needs...

## The Evolution of Drug-delivery Devices

***Pharma needs have evolved alongside the industry. Increasing efficacy and ensuring safety are no longer the only key goals of pharma, but today they also need to provide superior patient experience and collect evidence to support clinical and financial claims long-term.***



**Monitoring patient adherence and outcome during the drug's commercial phase** to support post-marketing surveillance studies and generate Real-world Evidence (RWE) and Health Economics Outcome Research data.

**Data-gathering and adherence-monitoring during clinical trials** to enable timely trial-design optimization and improve evidence generation.

**Improve usability and patient experience**, particularly for patients with condition-related impairments or for self-treatment at home, to differentiate similar molecules and drive patient compliance.

**Increase efficacy and ensure safety** of therapy administration, including the appropriate delivery of drugs with specific physiological aspects (e.g., viscosity) to support clinical claims and sustain pricing and reimbursement.

Source: Alira Health analysis

# … and to address major healthcare macro trends.

## The Evolution of Drug-delivery Devices

***Macro trends in the healthcare market, such as epidemiological trends, shifts in healthcare systems, and evolving trends due to new drugs' physiologies, are set to impact the need for innovative drug-delivery devices.***

### Rising prevalence of chronic diseases

The **prevalence of chronic diseases** such as asthma, COPD, cancer, and diabetes has increased significantly in recent years, particularly in **developing countries**, due to **lifestyle habits** (i.e, tobacco and alcohol consumption, diet, physical activity) and the **increasing geriatric population**.

Some of these conditions are drivers for DDDs, for instance insulin pumps for diabetes or inhalers for respiratory conditions' drug delivery.

### Shift to home care

The current pandemic and the need to remain home have **accelerated the development of home care** as an answer to the challenge for healthcare systems, including government and payors, to meet the expectations of an increasing number of patients **while being sustainable for healthcare systems.**

**Home care is** expected to provide **significant growth opportunities** for DDD players since such devices allow remote monitoring or self-injection, for instance, reducing the need for patients to attend healthcare facilities.

### Growth in the biologics market

There is an **increasing number of approved biologics**, which are often complex and highly viscous drugs requiring higher injection doses than currently marketed products.

This calls for the **development of new DDDs which can handle higher volume and viscosity, some of which can include electronic features.**

### Shift to value-based care

**Value-based payment models** focus on **measuring health outcomes** rather than the cost of delivering outcomes. They are driven **by pressure from governments, payors, and health authorities** to demonstrate outcomes.

Pharma companies are therefore receptive to this need from payors and try to develop better-performing devices or data-collection features that can support conclusions about the outcomes and thus **have a positive impact on the market**.

| IMPACT FOR THE MARKET | Rising prevalence of chronic diseases | | Shift to home care | | Growth in the biologics market | | Shift to value-based care | |
|---|---|---|---|---|---|---|---|---|
| | Today | In 5 years | Today | In 5 years | Today | In 5 years | Today | In 5 years |
| | HIGH | | MEDIUM | | LOW | | | |

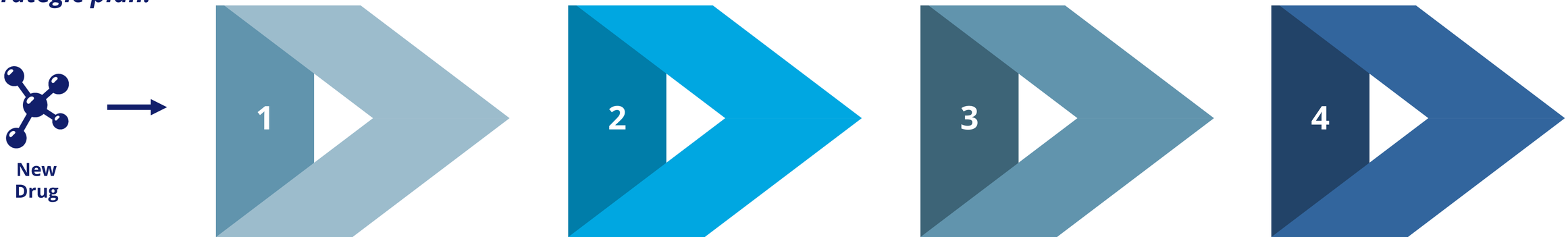
Source: MarketsandMarkets™, "Pharmaceutical drug delivery market," 2019; Landers, S., *The Future of Home Health Care*, SAGE, 2016; Deloitte, "The road to value-based care"; Alira Health analysis

# Section

# Pharma's DDD decision-making process involves various considerations…

## Pharma Decision-making Process

***Various factors are considered by pharma during their DDD decision-making process. Besides the selection of the appropriate delivery system for the therapy, pharma also evaluates the different options based on their internal capabilities and their long-term strategic plan.***




| | 1 DRUG PHYSIOLOGY | 2 PRODUCT DIFFERENTATION AND SETTING | 3 PLATFORM vs. PROPRIETARY DEVICE | 4 CONNECTIVITY |
|---|---|---|---|---|
| ***Key considerations*** | | | | |
| ***Key questions for pharma companies in the selection of a DDD*** | ▪ *What is the expected physiology of the drug (e.g., viscosity, volume, delivery rate, frequency of use)?*<br>▪ *What type of molecule is the drug (e.g., biologic, small molecule)?*<br>▪ *What is the safety profile of the drug and who will be the stakeholder delivering it?* | ▪ *What is the target patient population?*<br>▪ *What potential impairments could be addressed to improve usability and patient experience?*<br>▪ *Where is the DDD going to be used (clinical or commercial setting)?*<br>▪ *What is the targeted level of product differentiation? What type of device features are important and why? Which are must-have and which nice-to-have?* | ▪ *What is the planned time to market and budget?*<br>▪ *Can the DDD be developed in-house? If not, is there an already-existing DDD platform meeting required features, or does it need to be developed from scratch?*<br>▪ *In the case of going with a platform, what level of exclusivity is necessary?* | ▪ *Are there important unmet needs or high complication costs in my target population that can be addressed through a connected ecosystem?*<br>▪ *What is the maturity level of digital health in the target population?*<br>▪ *How could connectivity bring value to the company?*<br>▪ *What capabilities are required in-house and what needs to be outsourced?* |

Source: Alira Health analysis

# ...whether the device will be used in a commercial or clinical setting...

## Pharma Decision-making Process

***The setting in which the DDD is going to be used impacts pharma needs as it drives specific device developments according to certain features, whether in clinical-trial or commercial use, while ensuring satisfactory patient (user) experience.***

**Objectives of Commercial vs Clinical Trial Settings**

### Clinical Setting

- **Collect as much data** as possible to **prove efficiency** of the drug, understand patient behavior, and also **support filing to payors and regulators**
- Perform assessment of the **drug's interaction with the primary container** in order to **select the appropriate device**
- **Optimize the design of the DDD** for commercial settings. For some products, the clinical trial must already include the DDD that will be used in conjunction with the drug on the commercial stage
- Ensure the delivery system is **accurately releasing the proper dosage** into the targeted area for effective treatment
- Test biocompatibility to make sure the **device is safe for users** to handle with the drug, considering both direct and indirect user- interfacing elements

### Commercial Setting

- Provide **easy, convenient, and intuitive drug delivery** to the patient to create a confident user experience
- **Improve patient compliance and adherence, and ultimately experience,** to sustain treatment outcomes
- Select appropriate device material that **can maintain drug stability** over the product's shelf life
- Ensure **compatibility of the primary container** system with the selected device and manufacturing process
- Consider which device has **minimal regulatory risk** and will not prohibit the drug's go-to-market timeline
- Choose a device that is **easy for the patient to use** in a home-care setting without the intervention of a health-care provider
- **Collect RWE data** to support pricing and reimbursement

Source: Song, M., "4 Important Things to Consider Before Developing a Drug Delivery Device," 2019; Shortall, A., "Criteria for Selecting a Wearable Injector Technology and Partner," 2014; Alira Health analysis.

# ...the priorities to be met with the selection of a DDD...

## Pharma Decision-making Process

***The choice of a proprietary DDD vs. an existing platform by pharma will depend on the availability of existing DDD options and pharma's priorities. Platforms' main benefits are the reduction of cost and time at the expense of achieving greater differentiation.***

**Decision-making Criteria for Development of Proprietary DDD vs. Selecting an Existing DDD Platform**

### Advantages of Developing a Proprietary Product

**Develop devices that can adapt to the specific new drug types <u>not yet addressed by existing product platforms</u>:**

- Emerging biologics molecules are **highly concentrated and viscous** and require large volumes (greater than 1 ml).
- Determine the **compatibility of materials** to deliver small molecules and nanomedicine, as from a material perspective existing DDD may not have the appropriate polymers to ensure biocompatibility.
- **Facilitate reconstitution** as some lyophilized/liquid molecules need to be recombined before delivery and thus require double chamber systems.

**IP ownership** to protect the drug-device combination product from competitors.

**The ability to target specific patient groups** who need specific ergonomic designs to facilitate usability (e.g., handling via automatic needle insertion for osteoarthritis patients with reduced dexterity) does not exist as a platform and would require new DDD development.

As **connectivity** is a recent trend in DDD, some existing platforms do not yet include connectivity features. Some pharma, therefore, prefer to develop their own connected devices with specialized partners.

**Further differentiate in the market** through the selection of an innovative device with distinguishing features from available DDD (e.g., superior usability, connectivity).

### Advantages of Selecting a DDD Platform

**Reducing development costs** associated to new proprietary devices since costs are already amortized by the owner of the product platform. Pharma companies can save up to $3M when opting for a platform vs. starting a new concept from scratch.

**Accelerating time to market** (vs. proprietary development) as the first steps of development have been completed and the device master file might have already been submitted and pre-approved by regulatory authorities. With DDD platforms, pharma companies can reduce development time by 1-3 years on average.

**Leveraging a validated DDD platform to other pipeline candidates,** thus further reducing development costs and time and allowing pharma to focus its resources on core business (i.e., drug development).

Source: Alira Health analysis; Primary interviews

# ...and whether to add connectivity, depending on the goals.

## Pharma Decision-making Process

***The decision to incorporate connectivity in the DDD is linked to the type of therapy and the selected strategy and goals sought by pharma (e.g., achieving differentiation and collecting evidence to support clinical and economic claims).***

**Decision-making Criteria for Connected DDD**

***The decision to develop a connected DDD is linked to value-based considerations and the type of drug and strategy sought by pharma:***

### Sustain high-price therapy claims

- Enable **appropriate delivery of innovative drugs** with specific physiological aspects (e.g., high viscosity and volume) requiring electromechanical assistance
- **Capture data from clinical trials and RWE** to support clinical claims and justify premium price of high-value therapies
- **Ensure patients' compliance** and adherence as to **reduce disease-management costs**

### Increase value of low-priced therapies with high disease burden

- **Increase value** of low-price therapies by incorporating benefits beyond efficacy and safety of the drug
- **Improve patients' adherence and compliance** to limit associated costs (e.g., complications)
- **Promote home care** through data connectivity with healthcare professionals by optimizing healthcare resources
- **Collect RWEs to demonstrate health economic benefits** for the long term and sustain price and reimbursement in **value-based care models**

### Differentiate generic and biosimilars

- **Obtain differentiation from originators** by incorporating benefits beyond established efficacy, safety, and patient- experience standards

Source: "Medical Design & Outsourcing, Connected medical devices: What are the pros and cons?", 2018; Henderson, C., "New technologies for low-cost connected drug delivery devices," OnDrugDelivery, 2017; Primary interviews; Alira Health analysis.

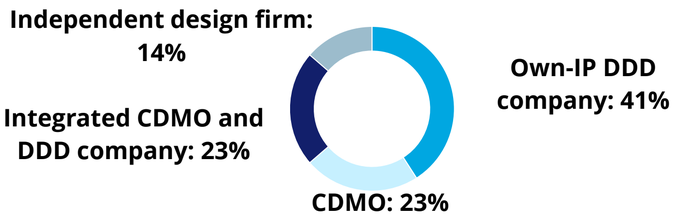
# Section

# Respondents' Typology Overview

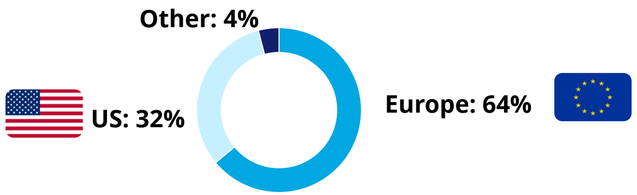
## Voice of the DDD Industry

***The survey yielded 22 respondents, 59% of which were C-levels and VPs in the concentrated DDD industry. CDMOs, own-IP platform-developers, and design firms were covered both in Europe and in the US.***

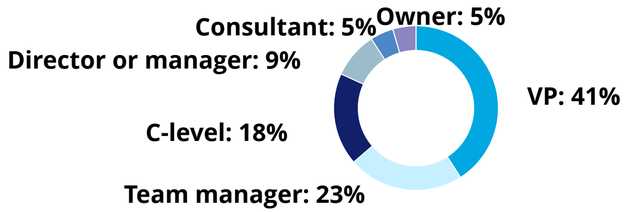
### Respondents' Repartition by Type of Company



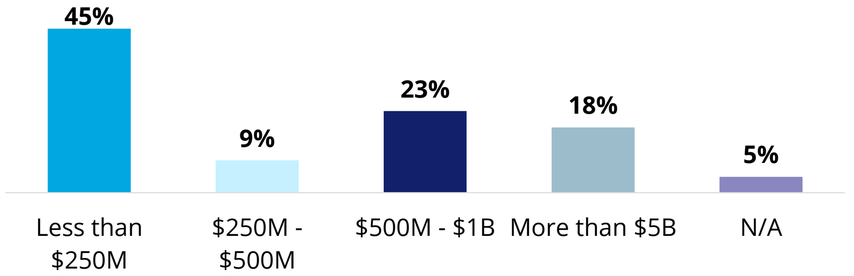

### Respondents' Repartition by Geography



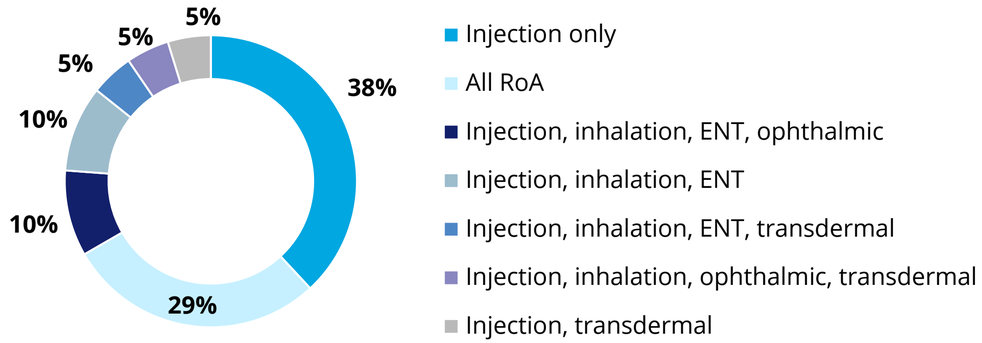

### Respondents' Repartition by Position




### Respondents' Repartition by Revenue




### Which of the following route(s) of administration does your company serve?[1]



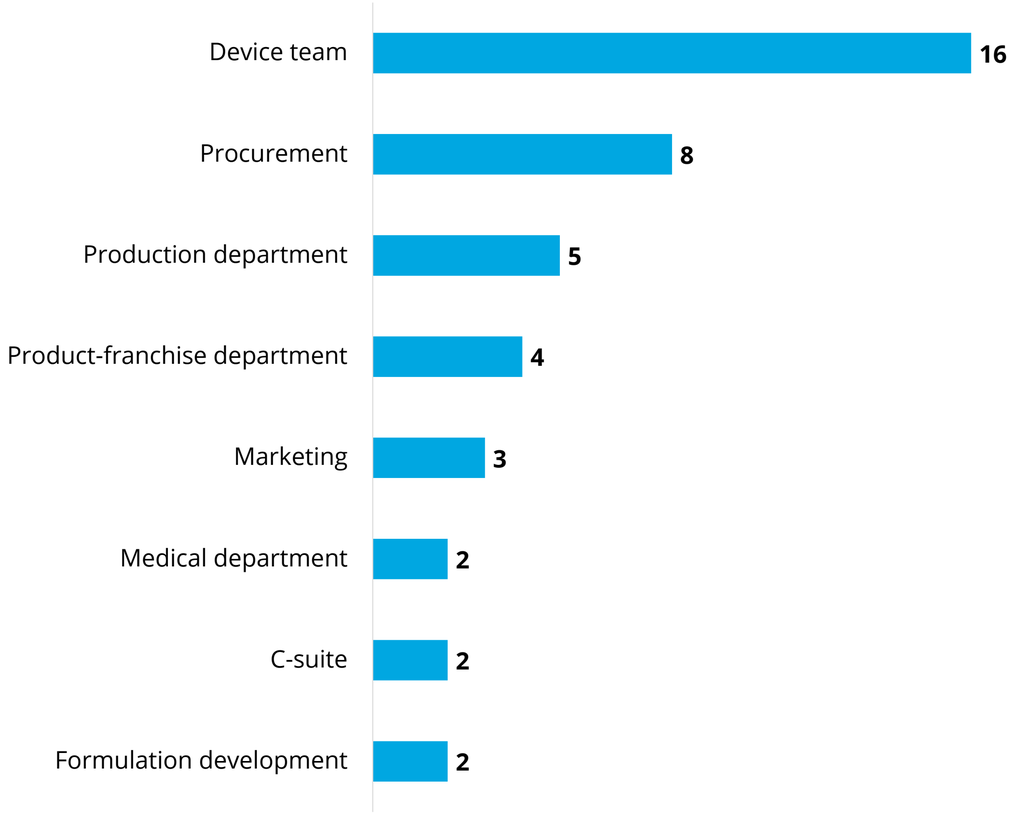

Source: Alira Health survey.

# DDD Players' View on Pharma Decision-making Process

## Voice of the DDD Industry

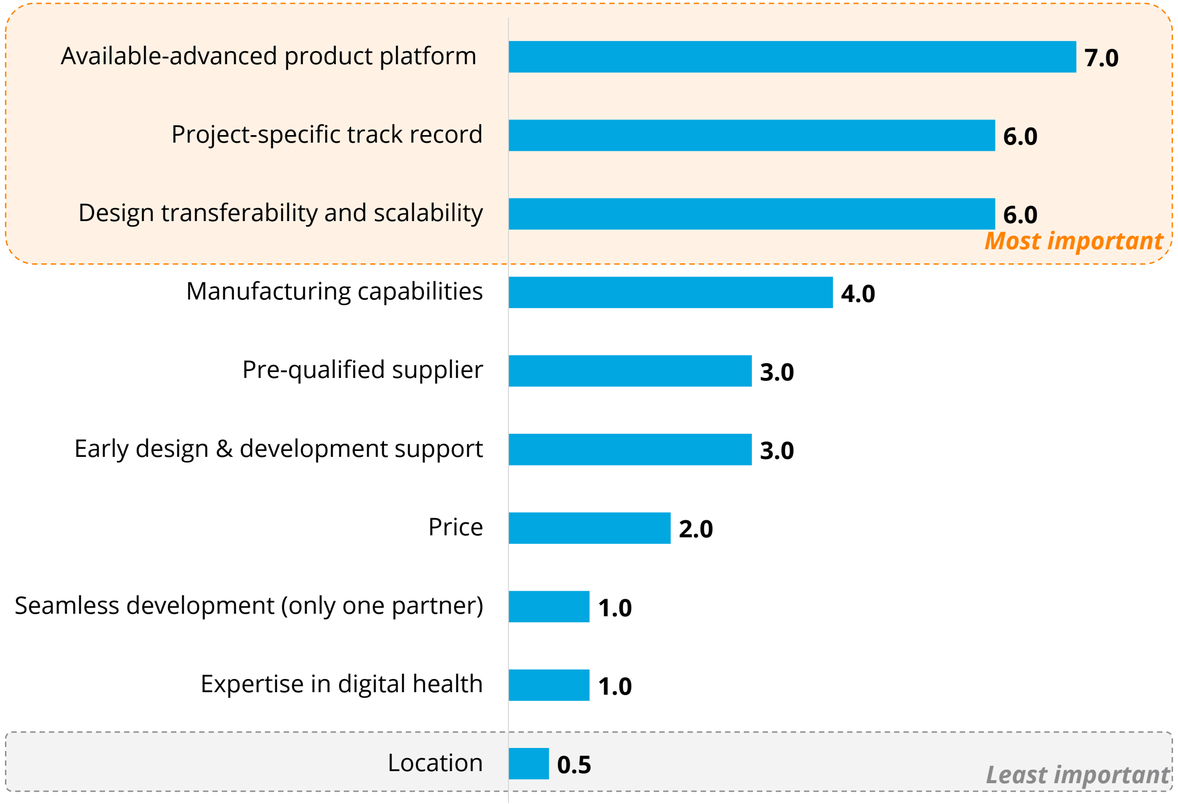
**Who are the decision-makers in the selection of the DDD in pharma companies?**

# Mentions by respondents:




**In the decision-making process to use a product platform, how important are the following to your clients ?**

# Mentions by respondents:

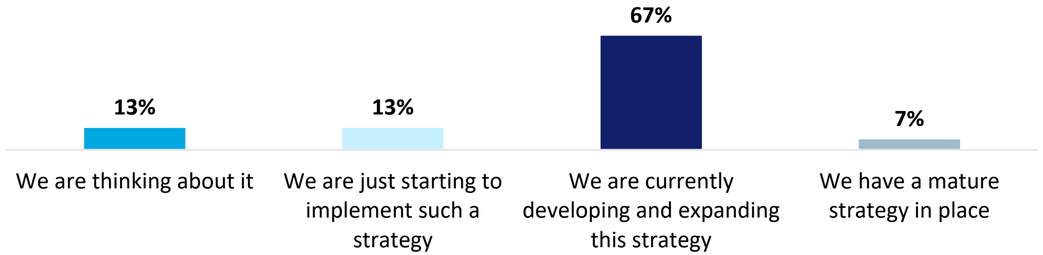



Note: [1]Several respondents are active in various RoA. Source: Alira Health survey.

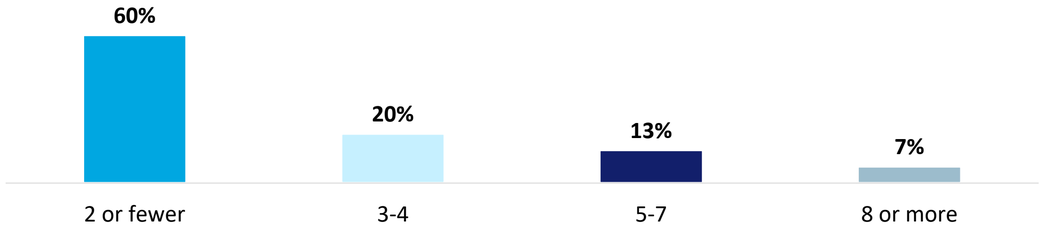
# DDD Players' View of their Digital-health Maturity

## Voice of the DDD Industry

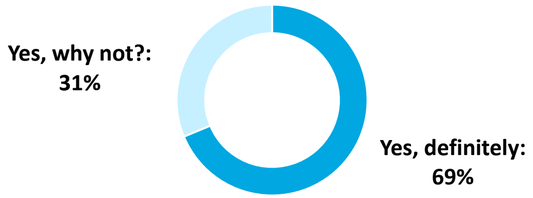
### How would you rate the maturity of a digital-health strategy within your company?




### Out of 10 new product developments, how many include connected devices/DH?



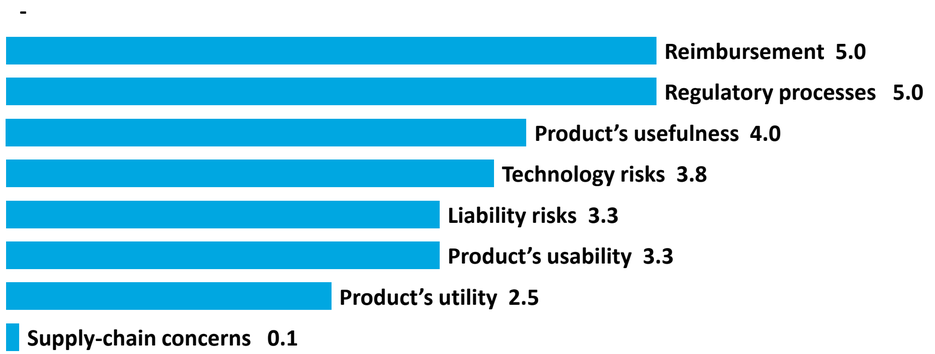

### Do you believe that CDMOs and DDD companies should play a role in assisting pharma in building digital-health ecosystems and monetization strategies?




Source: Alira Health survey.

### Barriers to developing or adopting a connected device and digital-health strategy

How would you score the following barriers for you and your clients to develop or adopt a connected device and digital-health strategy?
*(From 1-5 with 1 being not important and 5 very important)*




**Comment**

Product's usefulness, usability, and utility have been defined as follows (clarified for respondents):

- **Product's usefulness:** Can the product deliver clinical benefits through the use of collected data?
- **Product's usability:** Is the product convenient, safe, and easy to use?
- **Product's utility:** Can the product address the financial concerns of the providers and payors? What is its impact in health economics? Is there a monetization strategy behind it?

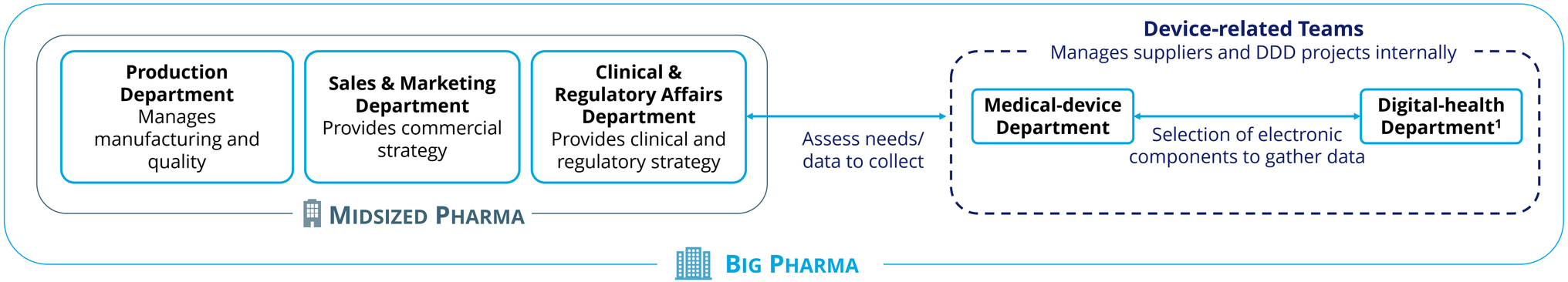
# Section

# DDD-related Needs of Pharma Vary, Depending on their Size

## How Pharma Needs are Addressed by Industry Players

***Both large and midsized pharmaceutical companies turn to DDD suppliers to fill certain gaps in their own capabilities. Whereas most needs are shared between the two groups, midsized pharma requires a more holistic umbrella of services from DDD suppliers.***

Based on the company's size, **certain capabilities** related to medical-device development, manufacturing, and commercialization **are not in-house**. This is particularly so for midsized pharma, while big pharma usually has its own internal medical-device and digital-health departments…




…**resulting in different capability and expertise** needs sought from suppliers.

### Midsized Pharma

- **Full integration** of capabilities (from conceptualization to logistics)
- **Small- and large-scale** manufacturing capabilities
- **Design-related competences** (including prototyping and design for manufacturing) to reduce early medical-device-related costs as well as time to market
- Life-cycle management of DDD products and **pre- and post-launch services** (e.g., regulatory support)
- Assistance in defining, developing, and commercializing a **digital-health solution**

### Big Pharma

- **Specific technical knowledge** to fill gaps in certain areas related to the drug delivery device (e.g., electronics)
- **Design-related competences** (including prototyping and design for manufacturing) to reduce early medical-device-related costs as well as time to market
- **Small- and large-scale** manufacturing capabilities

Note: [1]If the developed device requires digital health. Source: Alira Health analysis; Primary interviews.

# A Patient-Centric Injection-IP Owner: a Chat With Haselmeier

## How Pharma Needs are Addressed by Industry Players

### Interviewer Profiles

**Marco Linari**
CEO
***Haselmeier – a Sulzer brand***

HASELMEIER
A Sulzer Brand

### Company Profile

**Haselmeier** is a solution provider for subcutaneous self-injection devices, developing proprietary technology that improves therapy while placing patient comfort and the needs of customers first.

**HQ:** Stuttgart, Germany

**Key Highlights in DDD:**

**2020**
- Acquisition from Sulzer, a global leader in fluid engineering, to boost Sulzer's applicators division in healthcare.
- Medical-device master file from FDA for D-Flex product platform. The D-Flex can be integrated into an ecosystem consisting of the injection pen, a connected cap, a mobile app, and the Haselmeier data platform.

**2018**
- Partnership with Common Sensing, a Cambridge-based smart-injector monitoring and support solutions company, to develop smart- connected monitoring and support solutions for users of injectable medicines.

**Key Delivery Routes**

**Injection**

### Insights

**How would you describe Haselmeier's business model and strategy in the DDD space?**

- When we look at where we are today, we have a **strong IP stand in the classical pen market.** For patients, our innovation and IP position translate to a **positive injection experience**; for customers, this means that they **can rely on us and have freedom to operate.**
- We are convinced that this is a very good foundation. What we are aiming for now is to repeat this in other areas in order to expand our reach, **have a broader portfolio, and play with different customer requirements** (higher volumes, high customization). This is **supported by the recent acquisition by Sulzer, which brings scaling ability in manufacturing and financial means.**
- When customers thought about Haselmeier in the past, they would probably think IP, niche market, and pen injectors. In the future, they should think "for pipeline drugs in its entirety, this is the partner that will allow us to effectively deliver drugs while **improving the patient experience to the maximum."**

**How have you seen pharma needs and demand evolve in the DDD industry?**

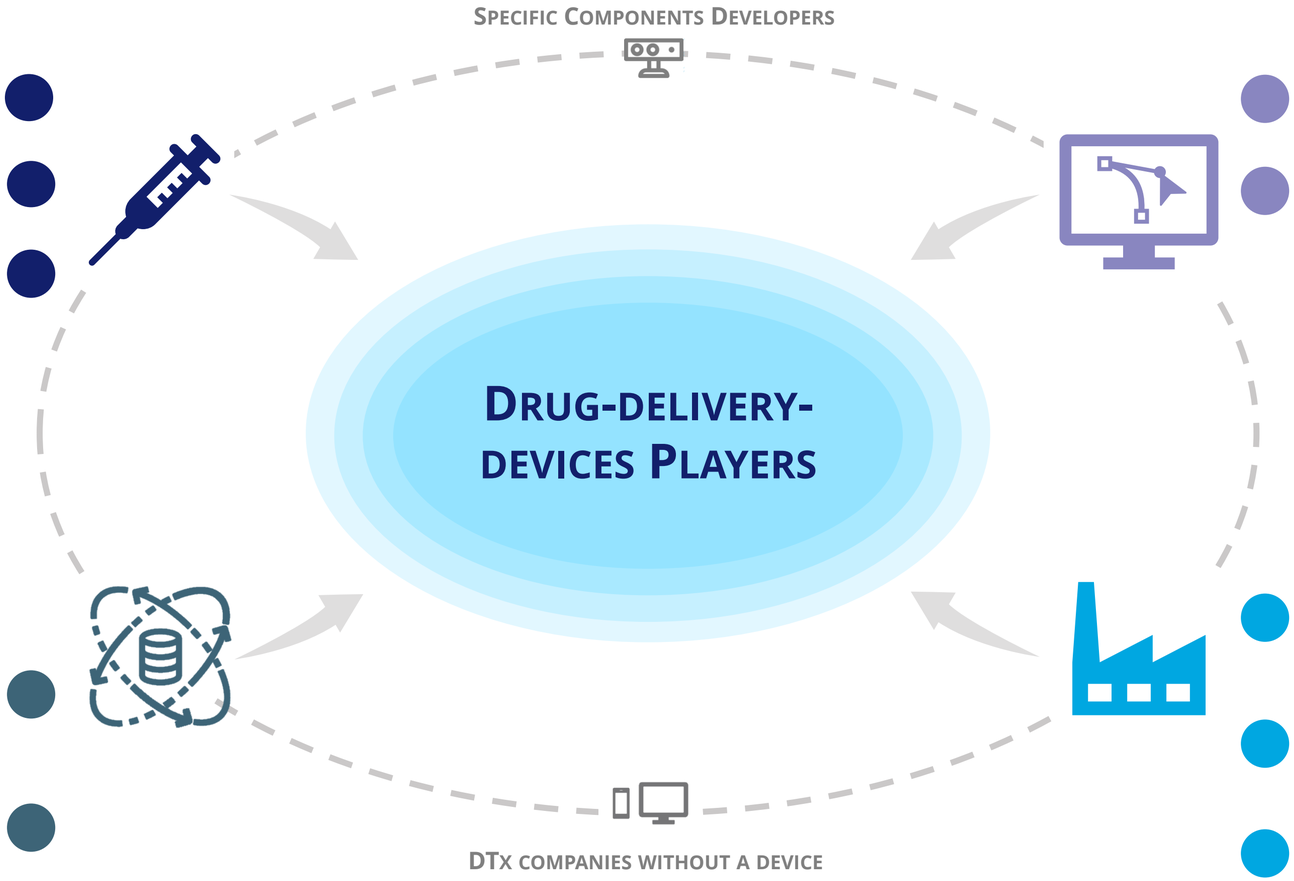
- **The most obvious need concerns flexible platform solutions, customization, and efficacy in drug delivery.**
- Furthermore, **connectivity is key**. If you talk to pharma about DDD platforms, they will tell you to **build devices that can be either mechanical or integrated within a digital solution.** Companies want to hold all options while finding their way forward in connectivity.
- While in clinical trials, the benefits of connectivity are easy to grasp; the **benefits in the outpatient market are shared between stakeholders** (patient, HCP, payors, pharma companies). The is no formula yet on how to address and split benefits, but everybody knows at one point it will come and drive the adoption and improvement of results. Therefore, **pharma companies want to be prepared for it**.

# Section

# Four main types of companies…

## Overview of the Competitive Landscape and Key Players' Positioning

***Own-IP DDD companies, CDMOs, and design firms intervene at different stages of the development and manufacturing of a DDD; they can work together as partners or as suppliers/customers. Other players are DTx companies, which mainly provide a digital solution.***




**DDD Platform / Own-IP Companies**

- Provide **products platform** ready for customization
- **Manufacture products** issued from these platforms **from clinical trials to commercial batches**
- Can also include **drug formulation services**

**DTx Companies with a device**

- Provide an **approved digital ecosystem** including connected add-ons, digital interfaces, cloud platforms, and data-modeling
- Provide **data analytics and modelling systems**

**Design firms**

- Provide **design & development**
- Can provide **prototyping and clinical batches manufacturing**

**CDMOs**

- Offer a large range of **services from design to large-scale manufacturing** as well as **formulation services**
- **Can provide specific capabilities** such as electronics components development and manufacturing.
- Provide **turnkey solutions** or allow to be leveraged on a **capability basis**

Source: Alira Health analysis

**Legend** — Players not included in this report's competitive landscape

# ...providing services in specific areas of expertise...

## Overview of the Competitive Landscape and Key Players' Positioning

***DDD market players can provide a wide range of services in traditional areas of expertise (i.e., related to design & development activities) or in new areas such as digital health and drug formulation.***

*Pure design-related activities* — *Production-related activities*

**Value Chain**

Opportunity identification → Design development → Design verification and validation → Design transfer → Small-scale manufacturing → Large-scale molding → Large-scale, automated assembly → Fill & finish

*Integration of services in new areas of expertise*

**Breadth of expertise areas**

***Traditional expertise areas***

**Human factors engineering**
Provide expert review analyses, usability testing, anthropometric analyses, and use-related risk management to develop a patient-centric device

**Conceptualization**
Understand market and user's needs to define opportunities and provide IP[2] mapping

**Prototyping & design transfer**
Develop prototypes and transfer design to manufacturing with system architecture and rapid visualization for manufacturing

**Regulatory support**
Provide product-development mapping, product-requirement documents, risk & hazard analysis, design history file

***Areas specific to digital health***

**Software and mobile apps development**
Develop digital platforms, including electromechanical components, user interfaces, AI systems, and analytics, as well as software-implementation support

**Electromechanical manufacturing**
Provide manufacturing of electromechanical components and assembly of connected devices for small and large volumes

**DH[1] management**
Manage digital ecosystem for pharma

***Area specific to drug formulation***

**Drug-formulation development**
Develop the drug formulation together with the DDD

Note: [1]DH: Digital Health; [2]IP: Intellectual Property Source: Alira Health analysis

# …compose the global DDD ecosystem…

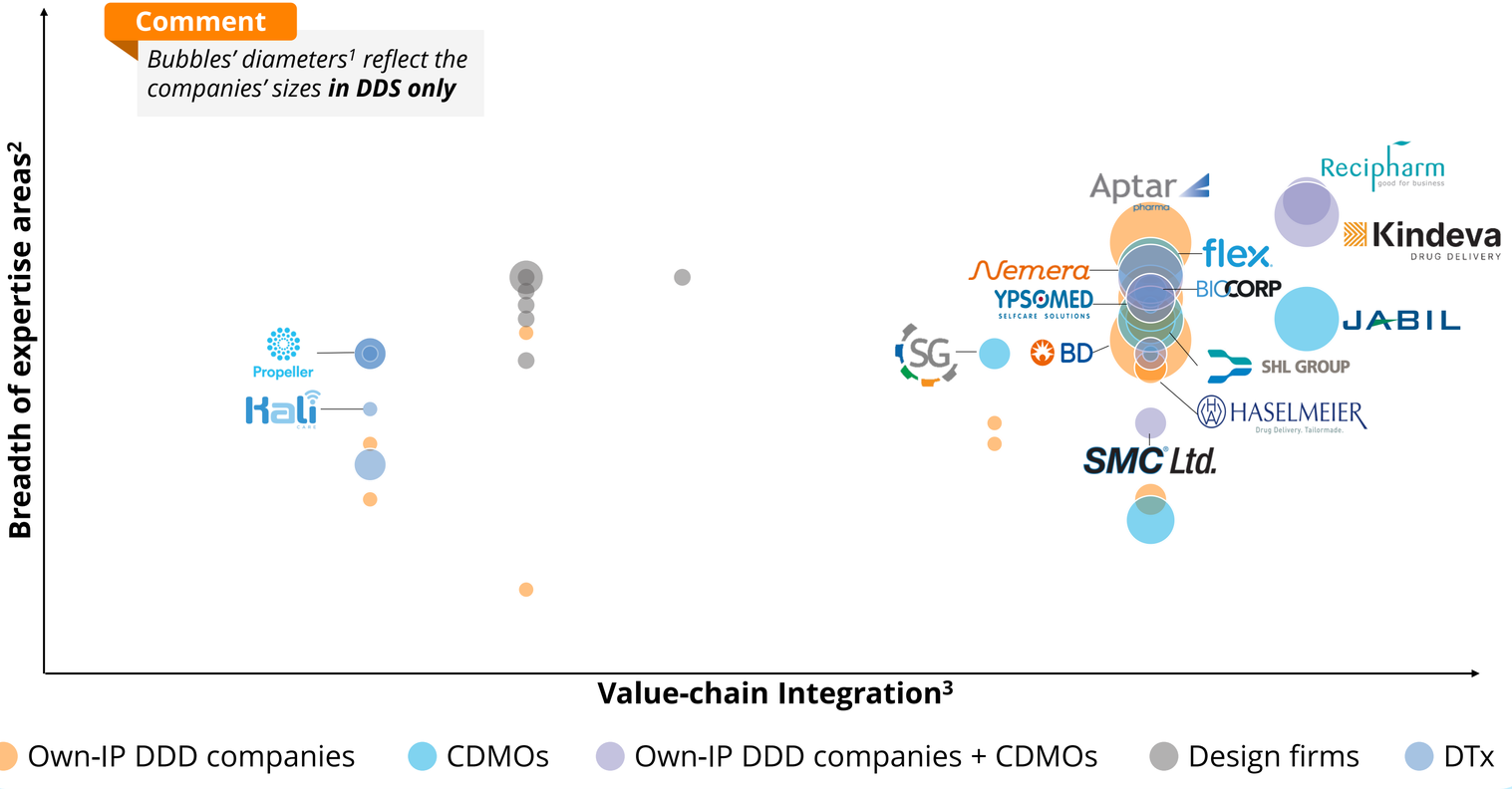
## Overview of the Competitive Landscape and Key Players' Positioning

***Players involved in the global DDD ecosystem have been segmented into 4 main categories: own-IP DDD companies; CDMOs; design firms; and DTx. A 5th category includes companies which are own-IP and CDMO at the same time.***

### Global-drug-delivery Ecosystem

**Comment**

*Bubbles' diameters[1] reflect the companies' sizes* ***in DDS only***



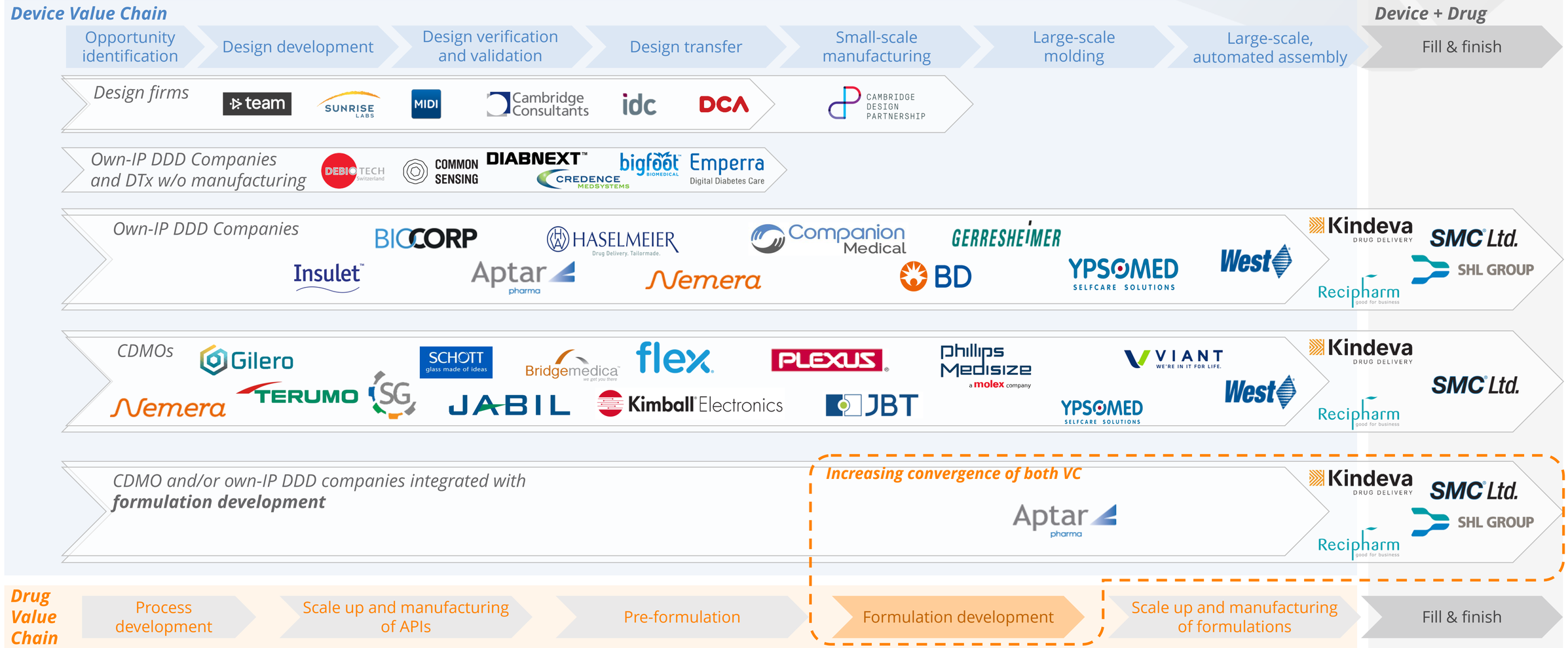

### Comments

- Close to **50 firms** in the global-drug-delivery ecosystem were analyzed. Players involved in the global DDD ecosystem have been segmented into 5 main categories: own-IP DDD companies; CDMOs; design firms; DTx; and companies which are own-IP and CDMO at the same time
- The firms are compared according to the **degree of vertical integration** in the device value chain (design & development and manufacturing capabilities), **breadth of expertise areas** (*cf.* previous slide) and **revenue.**
  - **Own-IP DDD companies** are integrated into the value chain and provide **diversified types of services depending on each company's capabilities** with or without manufacturing capabilities.
  - **CDMOs** offer a wide range of **services throughout the entire value chain** but do not own the IP of the products they develop and/or manufacture.
  - **Own-IP / DDD Platform companies + CDMOs** combine both business models.
  - **Design firms offer a broad set of design** and development services, but **without manufacturing capabilities** beyond prototyping and small-scale.
  - **DTx** companies provide **digital-health ecosystems which are associated to specific devices or agnostic.**

Note: [1]Company size is represented by the size of the bubble based on DDS sales ranges (<€10M / €10-100M / €100-400M / €400-1000M / >€1000M); [2]Breadth of expertise areas refers to the number of areas mentioned on page 29, that have been further weighted by categories; [3]Value chain integration refers to the value chain steps described page 29. Source: Companies' public information; Primary interviews; Alira Health analysis.

# ...with increasingly converging drug & device developments.

## Overview of the Competitive Landscape and Key Players' Positioning




Source: Companies' public information; Primary interviews; Alira Health analysis

# From Drug Formulation to Commercial Manufacturing: a Chat With Kindeva

## Overview of the Competitive Landscape and Key Players' Positioning

### Interviewer Profile

**Aaron Mann**
CEO
***Kindeva Drug Delivery***

Kindeva DRUG DELIVERY

### Company Profile

**Kindeva** is a global CDMO that brings the expertise, vision, and integrated end-to-end capabilities to develop and supply complex and combination drug products.

**Sales:** Private

**HQ:** Woodbury, MN, USA

**Key Highlights:**

- **2020** ▪ Spinoff from 3M to form Kindeva Drug Delivery
- **2018** ▪ First commercial solid microsystems agreement signed for treatment of osteoporosis with Radius Health
- **2016** ▪ Introduced the Intelligent Control Inhaler
- **2015** ▪ First generic combination asthma product in the UK
- **1995** ▪ First CFC[1]-free MDI
- **1969** ▪ First drug-in-adhesive patch
- **1956** ▪ First MDI

**Key Delivery Routes**

**Inhalation** | **Transdermal** | **Microsystems** *(Microneedles)*

### Insights

**What are Kindeva's key differentiating factors?**

- **Our integrated end-to-end capabilities.** Our customers get full value when they partner with us early in the value chain, from initial feasibility through formulation and development of complex drug/device combination products. There are many considerations (including quality, regulatory, and manufacturing) that emerge in the earliest stages that dictate success and speed downstream.
- **Our expertise in formulation and development.** As opposed to a pure CMO, Kindeva emphasizes both our development *and* our manufacturing capabilities. Kindeva has 300+ people in labs working on formulation and development of combination drug products. Many of our peers trace their business back to a manufacturing site, the core of their business; for comparison, our roots are planted in our applied-science legacy and sustained expertise.
- **Our track record of success.** We have completed the full formulation and development process more times than our closest peers. With over 20 product launches and decades of development and regulatory firsts, we help reduce risk over the entire life of our customers' products.

**What do you see for the future of Kindeva?**

- **There is an increasing interest in our microneedles-based solutions.** This platform has transformative potential to enable reproducible delivery to intradermal layers, promote self-administration of drugs, create savings for customers through dose-sparing, and eliminate cold chain in certain situations. This technology has potential for best-in-class delivery of vaccines, peptides, and other hard-to-deliver biologics.
- **Kindeva is developing a next generation of inhalation products.** Starting with industry-leading expertise in inhalation, Kindeva continues to work with its partners to develop cutting-edge innovations, ranging from connected inhalation solutions to more environmentally sustainable MDIs. We are developing products for systemic drug delivery to the lungs beyond asthma/COPD.
- **Kindeva is developing novel transdermal technologies.** Although applications for traditional drug-in-adhesive patches may be limited, transdermal is an important route for certain indications and patient populations. Innovations in areas such as gel patches and novel patch geometry can help differentiate our partners' product offering. In development, we apply human-centered design principles to enhance product performance and ease of use.

Note: [1]CFC: Chlorofluorocarbon

Source: Kindeva Drug Delivery, Legacy of Firsts, 2020; Primary interview; StarTribune, "3M completes $650M drug delivery unit sale, but business to remain in Twin Cities," 2020; Alira Health analysis

# Section

# DDD industry players are pursuing different integration strategies…

## Strategies Among DDD Industry Players

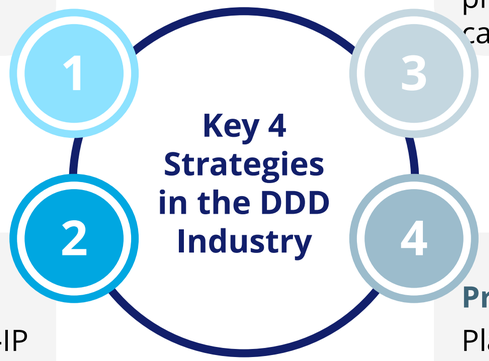
***Own-IP DDD players and medical-device and pharmaceutical CDMOs are continuously implementing strategies to provide turnkey solutions by integrating value chain and services.***

**Upstream integration of device-design development services by DDD CDMO players**

The addition of design services like conceptualization, user-centric design, and rapid prototyping has allowed DDD CMOs to engage with Pharma clients at earlier stages of the product lifecycle with the objective of converting them to large-volume manufacturing.

**Integration of early-stage drug development services by device manufacturer (and vice-versa)**

To differentiate their offering, provide turnkey solutions, and become partners from the earliest stages, own-IP and CDMO players are increasingly integrating early-stage drug development and formulation services. On the drug development side, pure pharmaceutical CDMOs are eyeing the integration of device capabilities.




**Acquisition of IP by CMOs and CDMOs**

CDMOs have started to develop, acquire, or in-license own-IP platforms to differentiate their offerings, collaborate with clients earlier, integrate the value chain, and capture more margins.

**Prospection of the digital health space**

Players are acquiring, hiring, or partnering to add connected solutions to their portfolios. They're developing specific capabilities like electronics, software, cloud architecture, and data analytics to stay competitive in the growing digital health space.

Source: Alira Health analysis

# …which are sometimes achieved through partnerships & M&A.

## Strategies Among DDD Industry Players

***DDD players have implemented these strategies organically or through partnerships/acquisitions.***

1

**Upstream integration of device-design development services by DDD CDMO players.**

Acquisition of Insight by Nemera

**2019**

Nemera, a DDD CMO, acquired Insight Product Development, a device-design firm, to strengthen its capabilities in DDD early-stage development and become an integrated CDMO.

*Other examples:*

2015 flex acquired farm

2

**Acquisition of IP by CMOs and CDMOs**

Acquisition of HASELMEIER by SULZER

**2020**

Sulzer acquired Haselmeier, a Swiss-German own-IP developer and manufacturer of injection drug-delivery devices. With this acquisition, Sulzer aims to complement its healthcare portfolio and leverage its expertise in precision-injection molding.

*Other examples:*

2019 Stevanato Group *exclusive license with agreement* HASELMEIER

2016 SMC Ltd. *acquired* OVAL MEDICAL TECHNOLOGIES

3

**Integration of early-stage Drug-development services by device manufacturers and vice versa**

Acquisition of GatewayAnalytical & nanopharm by Aptar pharma

**2019**

Aptar, an own-IP DDD provider, acquired Nanopharm, a provider of orally inhaled and nasal drug product-design and -development services, and Gateway Analytical, which provides predictive analytical services for injectable medicines.

*Other examples:*

2020 Recipharm *acquired* BESPAK

4

**Prospection of the digital-health space**

Acquisition of cohero by Aptar pharma

**2020**

Aptar acquired Cohero Health, a respiratory-management digital-therapeutics company, in 2020.

Source: Alira Health analysis

# Creating Value by Integrating a Pharma CDMO and a DDD Specialist: a Chat With Recipharm

## Interviewer Profiles

**Jean-Francois Hilaire**
Executive VP, Head of Strategy & Global Integration
***Recipharm***

## Company Profile

**Recipharm** is a world-leading pharmaceutical CDMO and own-IP DDD firm since the acquisition of Consort Medical and its DDD branch Bespak in 2019. The company supports customers from formulation development to fill & finish.

**Sales:** 2019 - SEK 7,457M (~$890M)

**HQ:** Stockholm, Sweden

**Key Highlights in DDD:**

**2020**
- Joint venture with Medspray, known as **Resyca BV,** to develop and exploit the soft-mist spray-nozzle technology for pharmaceutical applications

**2019**
- Acquisition of Consort Medical to **expand its capabilities by acquiring Bespak's DDD technologies and Aesica's formulation services**

### Key Delivery Routes

**Inhalation** | **Injection** | **ENT**

## Insights

**How would you describe the major trends in inhalation drug-delivery devices?**

- Until the early 2000s, when pharma was looking to recycle molecules, sophisticated inhaled formulations were mostly developed in-house by pharma.
- Today, most pharmaceutical companies **outsource the development and production** of **inhaled DDD because they are expensive**. Regarding drug formulation, it is very **difficult to launch a new inhaled formulation** because it requires **specific expertise** to assemble the device and the formulation, resulting in a growing trend toward externalization.
- **Both pharma and biotech** companies are looking for **integrated platforms** on which they can rely to easily develop new molecules for inhalation or **reformulate existing molecules** in this RoA, especially for molecules requiring rapid absorption, such as antidepressants.

**What is Recipharm's strategy and business model in the inhalation field?**

- Recipharm sought to **build capabilities and identify key services through the value chain** that helped build a consistent value proposition around inhalation.
- Last year, Recipharm acquired Consort with the objective of **acquiring the capabilities to adapt the device to the inhaled formulation** with Bespak's technologies.
- Recipharm's objective is to create a **reliable technology platform** that enables customers to **address all the challenges** and **reduce the complexity** associated with the development of inhaled DDD-based products ranging from formulation, design, and development to manufacturing and finally fill & finish with the objective of **accelerating time to market**.

Source: Primary interview; Alira Health analysis

# An Integrated CDMO and Own-IP Player: a Chat With Nemera

## Strategies Among DDD Industry Players

### Interviewer Profiles

**Marc Hämel**
CEO
*Nemera*

### Company Profile

**Nemera** is a world-leading drug-device combination solutions company and contract manufacturer with design and development capabilities as well as a full range of own-IP drug-delivery devices including asthma inhalers, insulin pens, autoinjectors, nasal pumps, and eye droppers.

**Sales:** ~ €436M (2020)

**HQ:** La Verpillière, France

**Key Highlights in DDD:**

**2020**
- Acquisition of Copernicus® to expand Nemera's proprietary product offering and manufacturing footprint in Eastern Europe
- Strategic partnership with Noble to incorporate a training-platform program with the Safe'n'Sound® injection system.

**2019**
- Acquisition of Insight to strengthen Nemera's design and development capabilities.

**Key Delivery Routes**

**Parenteral** *(Injection)* | **Inhalation** | **Ophthalmic** | **ENT** | **Transdermal**

### Insights

**How have you seen pharma needs and demands evolve in the DDD industry?**

- Pharma companies are looking for **holistic service providers** to **refocus on their core business** and, therefore, device companies like Nemera invest in technologies and manufacturing capabilities adapted to small- and large-scale manufacturing.
- Traditionally, devices targeted a large set of patient populations; however, there is **a need for devices targeted to specific needs** within smaller patient groups.

**What are Nemera's key differentiating factors to meet this demand ?**

- The ability to always think of the end user and the purpose of **putting patients first** really motivates the firm to provide the most effective solutions to its customers and patients.
- The **size of the company** which allows Nemera to be very agile and react quickly to any existing or new customer needs.
- The **service portfolio** around the device journey from early-stage design through to regulatory support and ultimately filling so the customers can concentrate on their core mission of inventing new medicines.

**What was the rationale behind the Copernicus acquisition?**

- Nemera acquired the injection devices manufacturer Copernicus at the end of October. The rationale behind the Copernicus acquisition was three-fold:
  - **Bolstering the overall proprietary product portfolio** and extending the injectable product offering
  - **Complementing Nemera's large-scale manufacturing** with Copernicus' fast and agile small-scale manufacturing
  - **Establishing an operations footprint** in Eastern Europe in order to build a new state-of-the-art manufacturing facility in Szczecin, Poland.

Source: Primary interview; Alira Health analysis

# Key Categories Identified across the M&A DDD Landscape

## Strategies Among DDD Industry Players

***Across the various partnerships formed in the DDD market, there were four main categories into which each transaction was further segmented: deal type; product type; route of administration; and therapeutic area.***

### Deal Type

**Co-development** deals involve the integration of each firm's unique offerings to allow for the development of a new product for the market.

**Portfolio expansion** deals include the purchase of a company offering a product outside of the acquirer's existing portfolio.

**Footprint expansion** deals allow for the acquirer to extend its reach into a new geographical area.

**Vertical integration** involves the acquisition of a company in a new part of the value chain to increase service offerings of the acquirer or streamline processes.

### Product Type

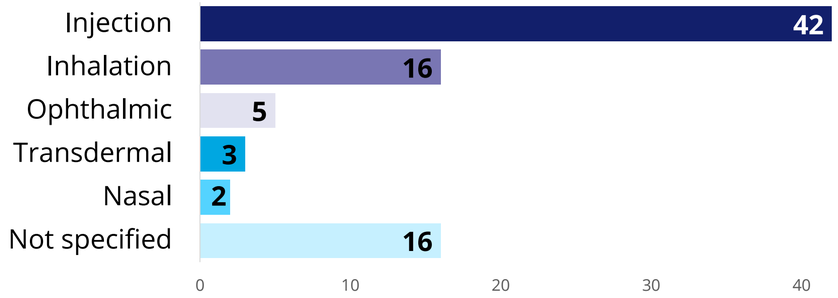
**DDD** category represents traditional drug-delivery devices without a digital component.

**Digital-health** segment includes DDD with a digital or connected component

**Digital-health/DTx** represents medical devices where the software is used to manage the medical condition.

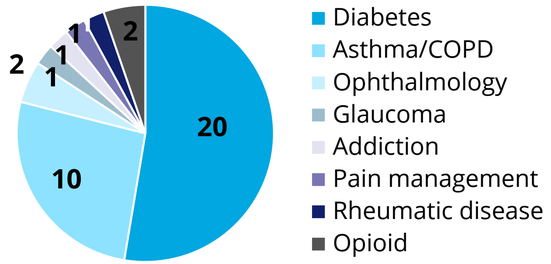
### Route of Administration (RoA)

Across the 84 acquisitions and deals analyzed, five RoAs were recognized with the remainder being unspecified.




### Therapeutic Area

38 of the partnerships and deals analyzed specified the therapeutic area the DDD would hope to treat. Diabetes was the clear leader across all therapeutic areas.




Source: Companies' public information; Alira Health analysis

# M&A Landscape by Deal Type

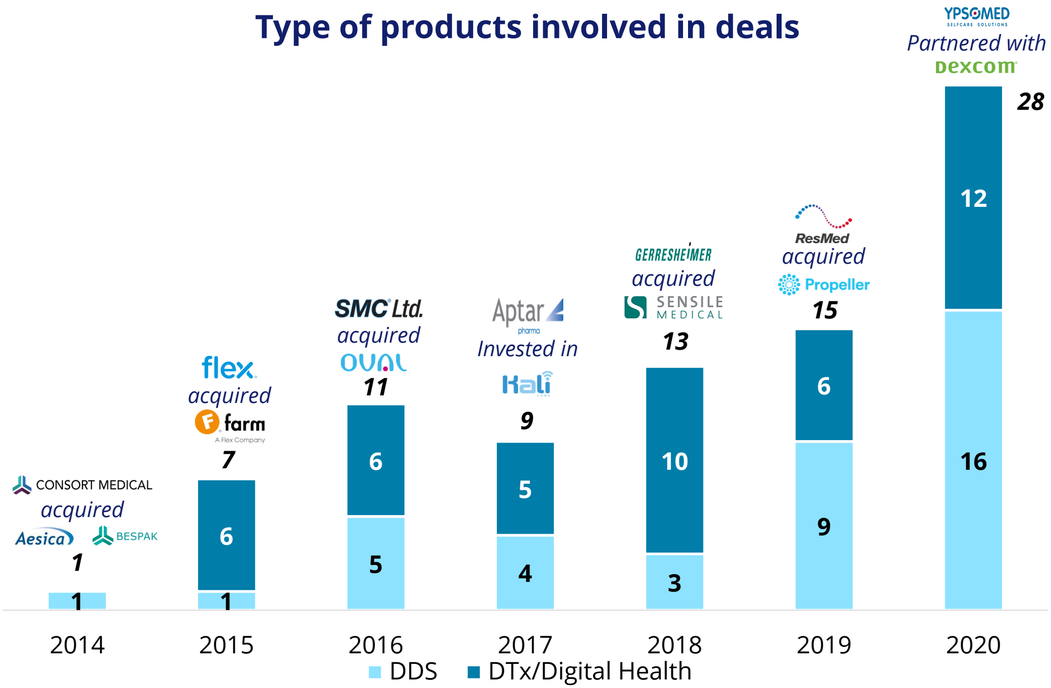
## Strategies Among DDD Industry Players

***Among selected relevant deals, strategic partnerships and M&A transactions are dominant, and deals that concern digital health are increasing over the years.***

### 84 Relevant Deals Selected[1] (2014-2020)

#### Type of deals


#### Type of products involved in deals




### Comments

- The **high volume of deals** in the DDD space has been a strong engine of the overall **industry consolidation trend**.
- More than half of the deals are **strategic partnerships**, usually for **co-development of innovative DDD**.
- **Transactions** are generally aimed at **the rapid implementation** of **corporate strategies[2].**
- More and more deals **including digital-health products** are taking place. As of 2019, **more than half of the deals were related to digital health**.

Note: [1]Alira Health selected 84 deals on the 2014-2020 period for further analysis; [2]Analyzed in previous section of the report

Source: Companies' public information; Alira Health analysis

# Examples of M&A Deals in the DDD industry

## Strategies Among DDD Industry Players

***Own-IP DDD companies are involved in many deals because they accelerate their vertical-integration strategy, such as Recipharm with Consort Medical; portfolio and footprint expansion; and/or to strengthen the digital-health strategy, such as ResMed with Propeller.***

Kindeva DRUG DELIVERY — 3M ALTARIS

*May 2020*

**Deal size = $650M**

**Sales**
3M (2019): $32.1B – Kindeva (3M DDD 2019): $406M – Altaris (equity capital): $4.9B

- Altaris Capital Partners acquired Kindeva Drug Delivery, formerly known as 3M Drug Delivery Systems, from the 3M Company. Kindeva is a leading **global CDMO** that specializes in solving complex drug-delivery challenges for its customers using **inhalation, transdermal, and microneedle drug- delivery technologies**.
- The acquisition enables the company **to build on its stand-alone business and a successful track record** as a leading provider of drug-delivery technologies.

Recipharm good for business — CONSORT MEDICAL

*November 2019*

**Deal size = ~$650M**

**Sales (2019)**
Recipharm: $7.5B – Consort Medical (Bespak Division): $165M

- Recipharm's acquisition of Consort Medical, a leading contract manufacturer of drug-delivery devices enables Recipharm **to complement its offering by acquiring drug-delivery know-how,** including the Bespak's technologies, in a **downstream value-chain integration effort** of high strategic-impact and synergistic potential.
- The acquisition enables the company to offer **integrated device-development and supply combined with commercial-scale manufacturing** of finished-dose products.

ResMed — Propeller

*January 2019*

**Deal size = $225M**

**Sales (2019)**
ResMed: $2.9B – Propeller: <$10M

- ResMed, a company specializing in cloud-connectable medical devices, acquired Propeller Health, **a DTx company which provides a digital-health platform for chronic respiratory diseases**.
- Propeller's digital-health solutions and partnerships (with pharmaceutical and healthcare organizations) **completed and strengthened ResMed's suite of products in respiratory care and digital-health solutions**.

Source: Companies' public information; Alira Health analysis

# Examples of Strategic Partnerships in the DDD Industry

## Strategies Among DDD Industry Players

***The DDD space is filled with strategic partnerships that did not include a formal merger or acquisition. For 2020, the focus of these partnerships centered around connected devices and assisting patients to adopt better medication adherence.***

*October 2020*

**Strategic Partnership**

**Sales (2019)**

BIOCORP: $10B – AARDEX Group: $5M

- BIOCORP, a firm specialized in design, development, and manufacturing of medical devices, has formed a strategic alliance with AARDEX Group, a leader in medical-adherence solutions.
- This **partnership will combine** BIOCORP's **connected add-on solutions** for drug-delivery devices with AARDEX's **Medication Event Monitoring System** (MEMS®) that will **both measure and manage medication adherence**.
- The first project will **integrate** BIOCORP's **Injay connected solution** for **pre-filled syringes** (PFS) to AARDEX's **MEMS adherence software** to target medicines delivered by PFS to address therapeutic areas including Rheumatoid Arthritis, Multiple Sclerosis, Ophthalmology, Psoriasis, and Cardiovascular diseases.

*May 2020*

**Strategic Partnership**

**Sales (2019)**

Ypsomed: $494M – Dexcom: $1.5B

- Ypsomed Group, a developer and manufacturer of injection and infusion systems in the diabetes space, has partnered with Dexcom, a leading provider of continuous glucose monitoring (CGM) systems.
- The **partnership will integrate** the **glucose values from** Dexcom's G6 **sensors** into Ypsomed's **therapy-management solution**.
- **The data** from the Dexcom CGM and mylife YpsoPump insulin pump **will be visible and consolidated into the mylife app**. The app will **alert users when glucose levels are too high or too low**. The data can also be easily shared with physicians and caregivers.

*July 2020*

**Strategic Partnership**

**Sales (2019)**

Ximedica: $62.8M – KeborMed: <$1M

- Ximedica, a leader in medical-device design and development, has partnered with KeborMed, the developers of a medical IoT platform, to enhance its capabilities to **develop connected medical solutions**.
- KeborMed's connected-care platform features a plug-n-play approach to offer partners a turnkey solution that helps **reduce cost and minimize the time to market** typically required to develop a connected medical device.
- Ximedica will leverage KeborMed's **cloud platform to incorporate connectivity into a wide range of its portfolio** of products across many medical specialties, from respiratory to surgical.

Source: Companies' public information; Alira Health analysis

# Section

# DDD evolved over time to include electronics and connectivity…

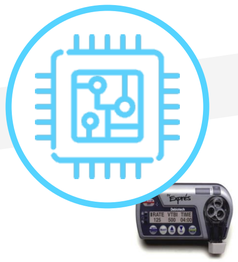
## Focus on Digital Health

***EDDD appeared about 20 years ago with electromechanical features that facilitated drug administration. Connectivity was then added to monitor patient adherence and other variables, first via add-on modules and then increasingly integrated into the device.***

Innovative features

### THE INTEGRATION OF ELECTROMECHANICS IN DDD

- **Improve patient usability** by integrating electromechanical parts into the device.
- Electromechanical DDDs improve the patient's self-administration of the drug by controlling administration time, dose, and adapted pressure, especially for injectable devices.



**Example of devices**

**Debiotech - Chronopump IV Express:**
Small and easy-to-use electromechanical infusion pump

### THE EMERGENCE OF CONNECTIVITY IN DDD

- **Improve patient compliance** through connected add-on modules providing dose counting or locking system functionalities.
- This phase started with add-on modules so companies could transition to the next phase.

**Examples of devices**

**Ypsomed - Smart Pilot:**
Connected add-on DDD suitable with pen injector YpsoMate

### THE RISE OF FULLY-INTEGRATED DEVICES

- **Improve communication between patients and HCPs and data-collection** by directly providing a fully-integrated connected device.
- This phase started in parallel with the previous one, as DDD players are still studying the benefits of a fully-integrated device versus an add-on module.

**Example of devices**

**Insulet – Omnipod®:**
Integrated, connected, wearable injector which allows patients to track insulin doses

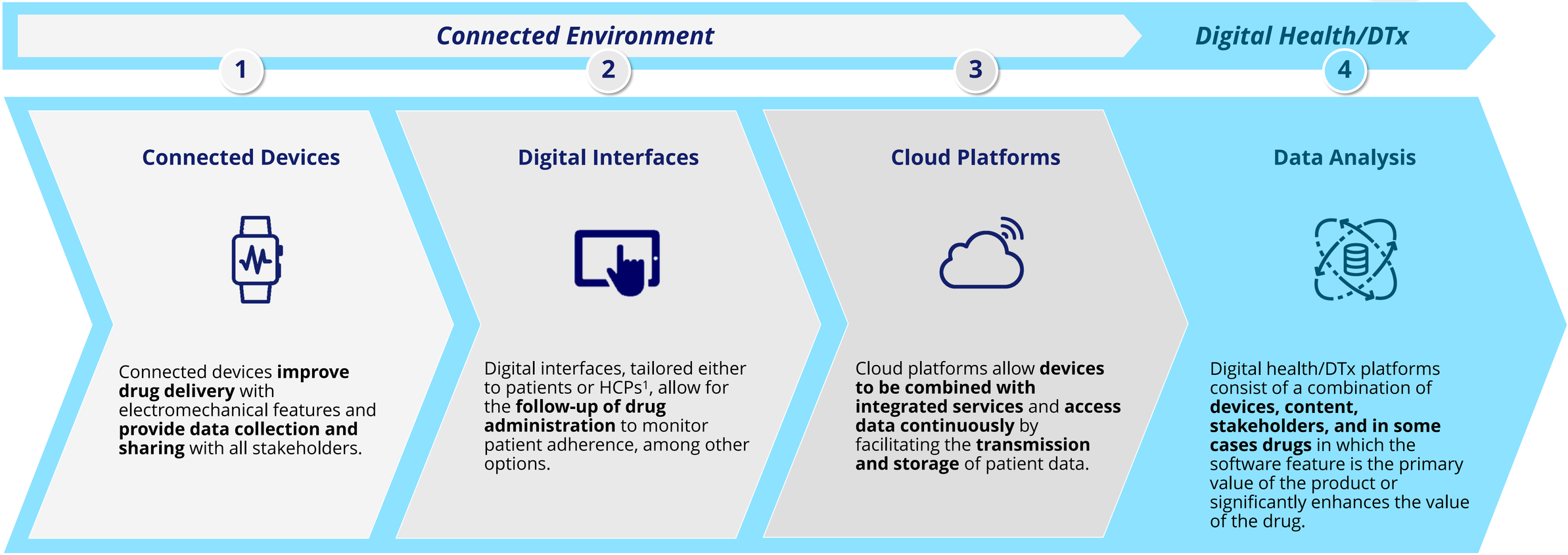
Time

Source: Primary interviews; companies' public information; Alira Health analysis

# ...to create an ecosystem with four main constituents.

## Focus on Digital Health

***Digital-health solutions/DTx encompasses connected devices, digital interfaces, and cloud platforms in an ecosystem composed of many stakeholders.***



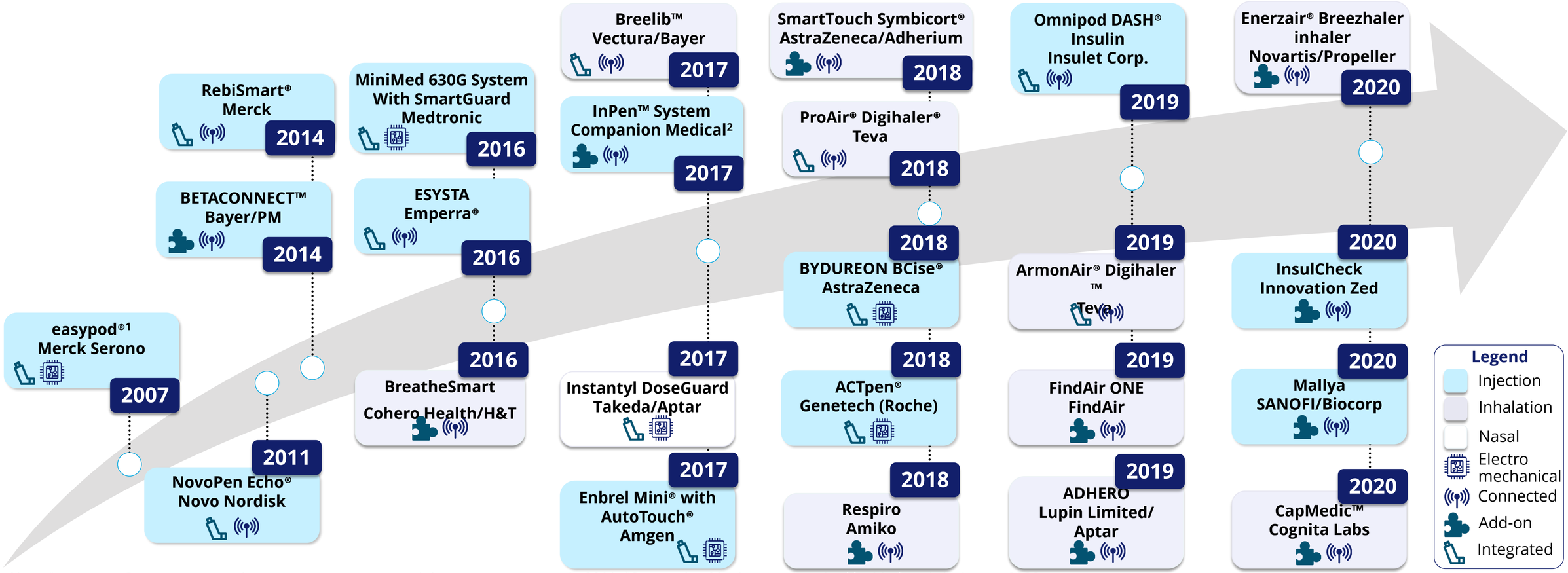

Source: Alira Health analysis

# Connectivity is still at an early stage…

## Focus on Digital Health

***Electronic and connected DDD appeared on the market about fifteen years ago. The RoAs with the most connected devices are mainly injectable and inhalation.***

### EDDD Marketed Products and Solutions (selected)




Note: [1] easypod® Connect, the app linked to the easypod® autoinjector, was launched in 2011; [2]Companion Medical was acquired by Medtronic in August 2020.

Source: Companies' public information

# ...as models still need to be defined...

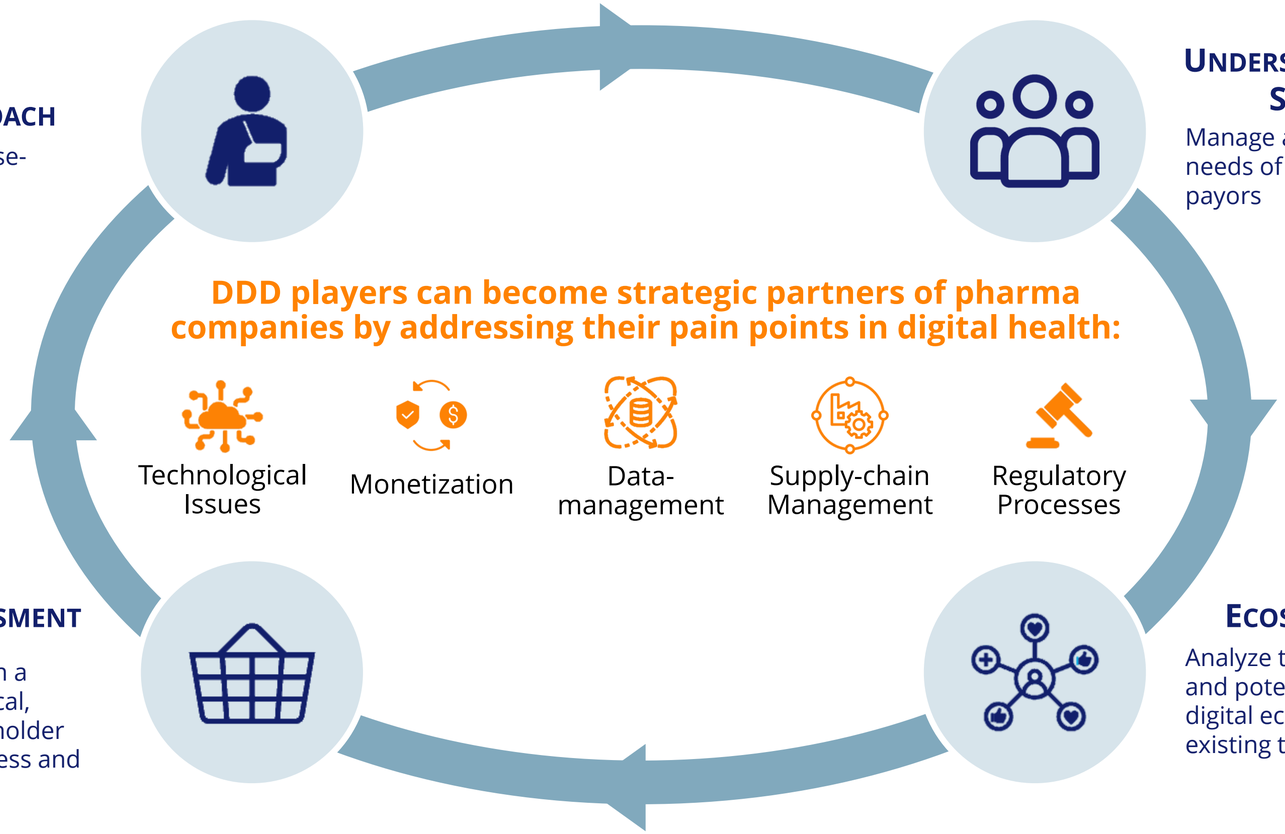
## Focus on Digital Health

***Developing connected DDD, which demonstrates outcomes for all stakeholders, requires the industry to establish new patient-centric iterative processes. DDD/Pharma co-development partnerships may be an ideal place to begin the creation of these new processes.***

### A connected DDD requires an iterative development process

**Patient-centric Approach**

Understand patient's disease-management and journey




**Understanding of Other Stakeholders**

Manage and consider unmet needs of HCPs, regulators, and payors

> "We try to make our solutions as simple as possible and ensure that we develop effective devices that meet patients' needs, but how can we manage the economics?"
> *Executive at a global CDMO*

**Market-Potential Assessment**

Assess the potential market from a perspective of competition, clinical, regulatory processes, and stakeholder engagement to define the business and monetization model

**Ecosystem Analysis**

Analyze the current suppliers and potential customers in the digital ecosystem as well as existing technology solutions

Source: Alira Health analysis

# ...to involve several healthcare stakeholders...

## Focus on Digital Health

***Patients are the end users of digital-health platforms and they also hold the decision power about whether to adopt them. Buyers and influencers act more as channel partners for the providers in order to make patients aware of and gain access to the platforms.***

**PROVIDERS**

Sell products and/or services for better healthcare outcomes while gaining access to healthcare data

**Medical-technology Companies**

Provide the platform

**Pharma Companies**

Provide the platform

**Tech Providers**

Connect to medical data

**USERS**

Actually use the solution to:
(1) Monitor and self-manage their conditions
(2) Review patient data with the goal of improving health outcomes.

**Patients**

Access convenient and easy-to-use information about their own healthcare

**Healthcare Professionals**

Are part of a connected healthcare environment

**CLINICIANS**

Increase diagnostic and treatment speed and improve clinical efficiency

**Healthcare Professionals**

Add value to their businesses

**Clinics/Labs**

Interface to existing clinical systems

**PAYERS**

Decrease healthcare costs and improve long term outcomes.

**Commercial Payors**

Offer a secure way of entering, outputting, and matching data

**Government**

Accesses overview of epidemiology insights

Source: Alira Health analysis

# ...to overcome barriers to patient adoption...

## Focus on Digital Health

***Patients are the end users of digital-health platforms and they also hold the decision power about whether to adopt them. Connected DDD require integration into a complete ecosystem to be adopted at a high rate and continually engaged with by patients.***

### Key Barriers to Adoption

**USER EXPERIENCE**

- Lack of communication
- Lack of value add
- Difficult to understand
- Manual/high effort

**Digital health sees particularly high dropout rates ranging from 25% to 65%**

### Methods to Surpass Barriers to Adoption

**1 Usability**

- **The usability for the end consumer of the product** is key to keeping their engagement high and ultimately adding value.
- **User-centric design** ensures the product is **convenient, safe, and easy to use** to allow easier adoption by the patient.

**2 Usefulness**

- The ability of the product to **deliver clinical benefit with the collected data** to personalize the delivery of pharma solutions or to increase the patient adherence.
- The patient must **experience improvement** to continue engagement with the digital-health product or service.

**3 Utility**

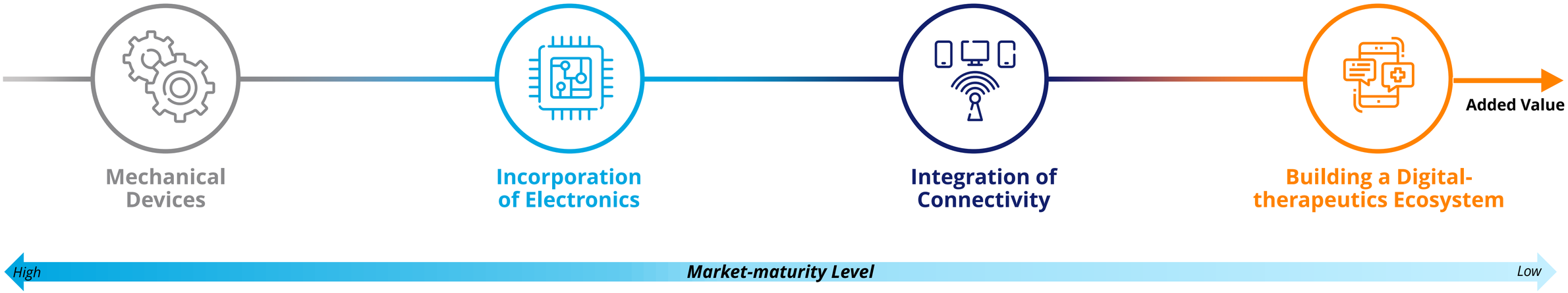
- The **positive impact in health economics** resulting from the use of the connected device.
- Utility addresses the **financial concerns of the providers and payors.** A product that is both usable and useful may not find market adoption without aligning to this requirement.

Source: Williams, C., Rafiei, R., and Howald, R., "Digital Health reformulation: from Hope to Hype to Health," ODdrugDelivery, 2020; Tison, G et al., "Achieving High Retention in Mobile Health Research Using Design Principles Adopted from Widely Popular Consumer Mobile Apps," 2018; Research2Guidance, "Impacting Behavioural Change: Which Concepts Work For mHealth?," 2018; Alira Health analysis

# ...and create value.

## Focus on Digital Health

***Added value grows correlatively with patient-centricity and digital-health integration. DDD market players need to integrate the digital-health market by helping pharmaceutical companies develop patient-centric devices.***




To **remain competitive** in the market, DDD players must not only **integrate the digital-health market,** but also **differentiate their products and services** from other competitors through:

- **Integrating further digital-health ecosystems**
- **Adopting more patient-centric models**
- **Assisting pharma (particularly midsized) in building new digital-health solutions**

Source: Alira Health analysis

# Digital-health Strategy by a DDD Leader: a Chat With Aptar Pharma

## Focus on Digital Health

### Interviewer Profile

**Patrick Jeukenne**
VP Strategy, BD and Marketing
***Aptar Pharma***

### Company Profile

**Aptar Pharma** is a leader in the DD space, fully integrated in AptarGroup Inc., a leader in drug delivery, consumer-product dispensing, and active packaging solutions. The company offers customized development services, manufacturing services, and regulatory, testing and post-launch support.

**Sales Aptar Pharma:** $1.2B (2019)

**HQ:** Crystal Lake, Illinois, US

**Key Highlights in Digital Health:**

- **2020** ▪ Acquisition of Cohero Health to strengthen Aptar Pharma's digital portfolio.
- **2018** ▪ Equity investment in Propeller in order to develop digital-medicine platforms.
- **2017** ▪ Equity investment in Kali Care to make clinical trials more efficient by combining Aptar Pharma's technologies and Kali Care's smart sensors.

**Key Delivery Routes**

**Injection** | **Inhalation** | **Ophthalmic** | **ENT (Nasal)**

### Insights

**How would you describe the digital-health market involving DDD?**

- The level of maturity is such that **today everyone can make a connected device for a reasonable cost.** This part of the technology is no longer a barrier.
- The **main barrier to adoption is linked to the many actors involved in the development and management of digital-health platforms.** Many suppliers are working on parts of the solution (i.e., one firm is working on the connected device; another on the software and/or app; another one on data analytics; etc.) and the question is how to integrate all the parts into one efficient platform.
- Many pharma companies do not develop **digital-health solutions by themselves** because they don't want to work with so many different suppliers and **prefer to have a third party that manages** the development and integrates parts into one integrated solution.
- **Within pharma today, there are multiple models being tested around digital health with the key questions centered around outcomes and who will be the payor.**

**What is Aptar Pharma's operational strategy in the digital-health field?**

- Aptar Pharma has a **wide range of connected devices through different RoAs**, either integrated or add-on devices.
- **Aptar Pharma wants to be the preferred integrator for pharma customers by managing the entire development of the digital-health platform** with other players. The company is well positioned to provide the entire solution and to carry out this integrator strategy through partnerships, equity investments, or acquisitions.
- **The Aptar Pharma digital-health team oversees this strategy.** It is led by Aptar Pharma, but it is like a startup with its own budget, free to make its own decisions.

Source: Primary interview; Alira Health analysis

# Market Trends and Digital-health Strategy by a CDMO: a Chat With Flex

## Focus on Digital Health

### Interviewer Profile

**Riccardo Butta**
Senior Vice President
***Flex Health Solutions***

### Company Profile

**Flex** is a global leader in design, engineering, manufacturing, and supply-chain solutions serving a number of different industries. **Flex Health Solutions** is a leading CDMO in the DDD space with extensive capabilities and experience in **injectors, inhalers, pumps, and connectivity modules**.

**Sales Flex:** $26.3B (2019)

**HQ:** Singapore

**Key Highlights in Digital Health:**

- **2020** ▪ Expansion of technology integration. Development of low-cost connectivity-module platform for injection pens.
- **2018** ▪ Multiple additional partnerships with leading pharma on joint development.
- **2017** ▪ Creation of BrightInsight digital-health platform designed under complete design controls. Subsequent spin-out in late 2019.
- **2016** ▪ Partnership with Enable Injections, Inc. to design, develop, and produce customized wearable injector systems.
- **2009+** ▪ Establishment of centers of excellence in technology development and integration support for our design centers.

*Flex is RoA-agnostic*

### Insights

**How would you describe the major trends in the DDD industry over the past years?**

- The first trend is **the addition of sensors and electronics to turn mechanical devices into smarter solutions** (e.g., adding sensing capabilities to enable dose-counting and facilitating improved patient adherence, ultimately leading to better outcomes).
- A second trend involves the wave of biologics coming to market and the need for different delivery mechanisms for their higher-viscosity, larger-volume. and therapy-specific requirements. This sustained the idea to **combine these large-molecule formulations with electromechanical devices**, allowing pharma companies to offer improved user interface, sensing capabilities, programmable delivery profiles (e.g., dosage, delivery rate), and connected solutions to their patients.
- The third trend is the rapid expansion of digital health, not only with sensing and connectivity features inside the device, but to include **end-to-end solutions to capture, transfer, store, and manage data to improve clinical outcomes.** This fuels the need for integration of connected devices, cloud infrastructure, data analytics, and mobile applications, all within a regulated and fully compliant ecosystem. Connected electromechanical devices for biologics will remain a minority share within the overall injectables market in unit volume (vs. insulin pens), but their **weight in value is increasingly significant and will continue to grow** in the coming years.

**What is the story of BrightInsight?**

- BrightInsight is a solution which **enables users to capture and transmit data, integrating the device within the cloud environment**. The solution is fully regulated and has earned a high-trust designation for privacy and safety.
- Organically, we incubated BrightInsight to its development. In 2019, we made it a stand-alone company, while remaining a shareholder, to allow it to grow faster. We are a major shareholder.

**What is Flex's main differentiator in the electronics and digital-health markets?**

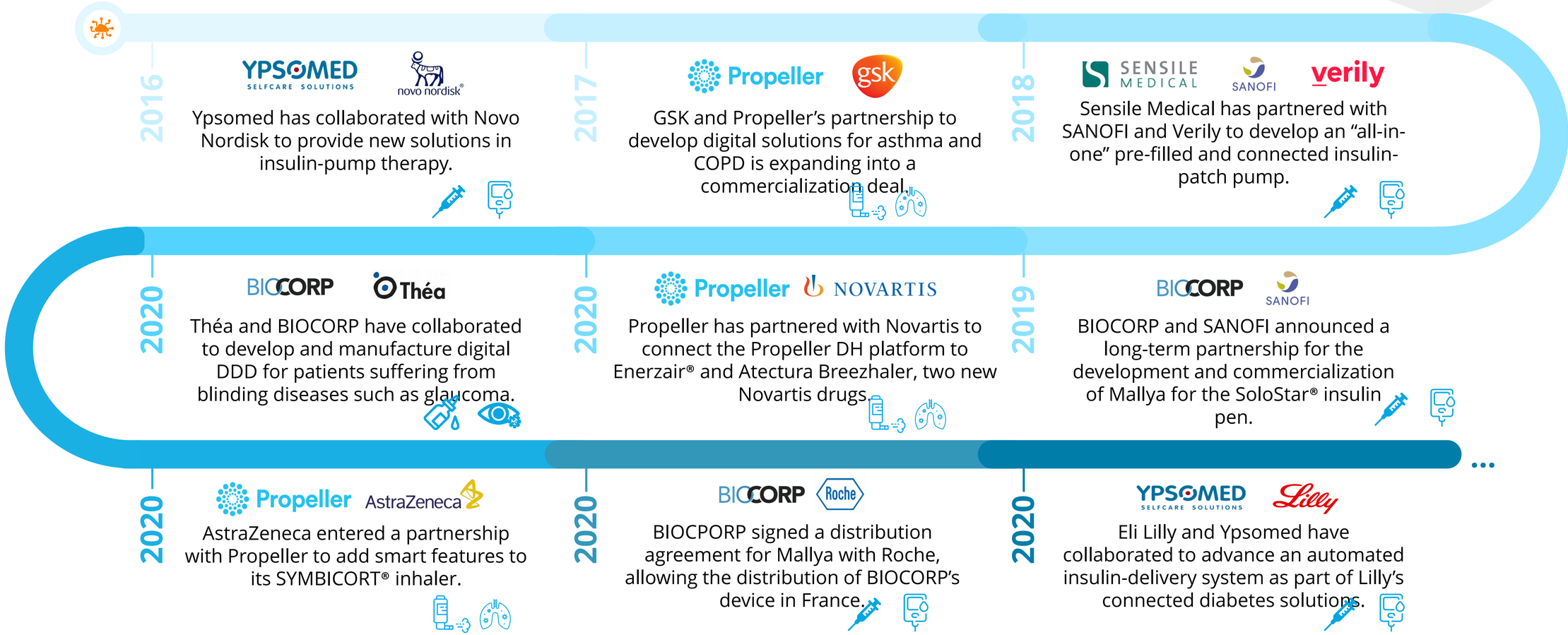
- **It's in the combination.** We have 20 years of proven **development and manufacturing experience** in devices plus expertise in **leading-edge technologies** from multiple industries, combined with **established supply-chain solutions** and vertically-integrated factories to enable fast, cost-effective scale-up. On the infrastructure side, we have **ready-to-go data-management** and software-development capabilities.

Source: Primary interview; Alira Health analysis

# Recent Transactions in DH Demonstrate the Interest of Pharma

## Focus on Digital Health

***Since 2016, pharma companies are developing more and more strategic partnerships with own-IP DDD companies in order to accelerate the development of connected devices for their medicines.***



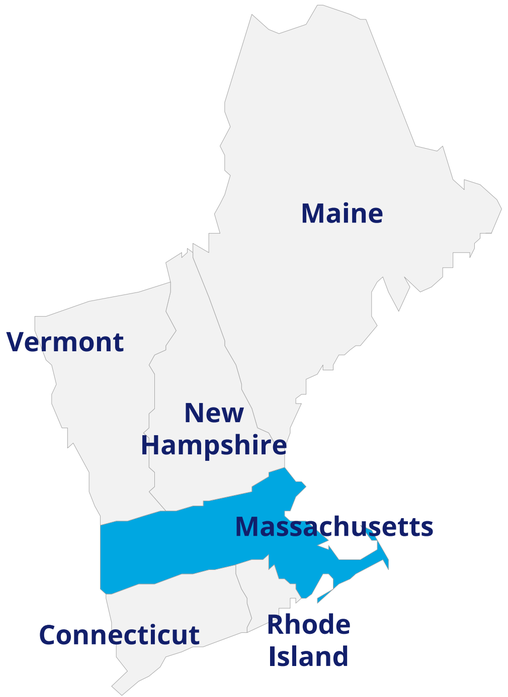

Source: Companies' public information; Alira Health Analysis

# Section

# New England: a Leader in Drug-delivery Devices

## New England's Global Appeal to Foster Collaboration Between DDD and Pharma

***The New England region is made up of a large community that can support and develop drug-delivery-device innovations. A strong pool of talent from local universities, pharmaceutical companies, and relevant adjacent manufacturers are some of the key factors.***




**1. Rich Community of Related Industries Drive DDD Innovation.**

- There has been significant progress in DDD research over the last five years, driven by the advancements in the pharmaceutical industry, biomedical research, and material sciences.
- There is a wide variety of organizations across New England, including specialized-material manufacturers (from polymers to tubing), five of the largest global pharmaceutical companies, and nationally recognized biomedical research hospitals, such as Baystate Health.

**2. Large Pool of Specialized Workforce**

- Throughout New England, there is a high concentration of prestigious universities that include specialized engineering programs to support development and innovation for the DDD market.
- The University of Massachusetts (UMass) has one of the world's largest academic centers for polymer research: the Polymer Science and Engineering Department.
- MIT (Massachusetts Institute of Technology), WPI (Worcester Polytechnic Institute), University of Connecticut - Institute of Material Sciences, Northeastern University, and Western New England College are other universities that foster a large pool of highly qualified talent.

**Why is New England a large market opportunity for drug-delivery devices?**

1. **Strategic Location:** Over 300 medical-device companies can be found along the Interstate-91 corridor that cuts through Connecticut and western Massachusetts. Access to Boston, New York, and top-tier universities and hospitals create this rich medical community.
2. **History of Precision-manufacturing:** New England has a strong history of precision-manufacturing for metals, plastics, and electronics - important expertise and support needed for DDD development.
3. **Higher Education and Research:** New England has one of the highest concentrations of hospitals and research universities which require continued advancements in DDDs to pair with innovations in drugs, bioresearch, etc.

Source: Li *et al.*, "Recent progress in drug delivery," 2019. MD+DI, "Medical Device Suppliers in New England," 2005; Western Mass News, "Medical Devices," 2018; Walker, "The Medical Devices Industry in Southern New England's I-91 Corridor," 2004

# Massachusetts: Where Drug-delivery Devices, Design, & Pharma Converge

## New England's Global Appeal to Foster Collaboration Between DDD and Pharma

***Massachusetts is made up of medical-device companies, design firms, and pharmaceutical companies all converging in one location to spur innovation and growth for the industry.***

**More than a dozen CDMOs** focused on **DDDs** with strong support from local design firms create an environment for **DDD innovation.**


**Boston – Cambridge**
**500+** biotech and life sciences companies
**$6.5B** NIH and VC funding (2019)

**Over 400 medical device and 700 life sciences companies** can be found across the **state of Massachusetts** and expanding into the surrounding states

**2nd state in the US for 510(k) clearances**
*(after California)*

**Five** of the **top ten global pharmaceutical** companies have presence directly in Massachusetts

Source: BioSpace, "Top 20 Pharma Companies by Market Cap in Q1," 2019; Grant Thornton, "Medical Devices in Massachusetts State of the Industry," 2019; CBRE, Boston Life Sciences 2020; Alira Health analysis

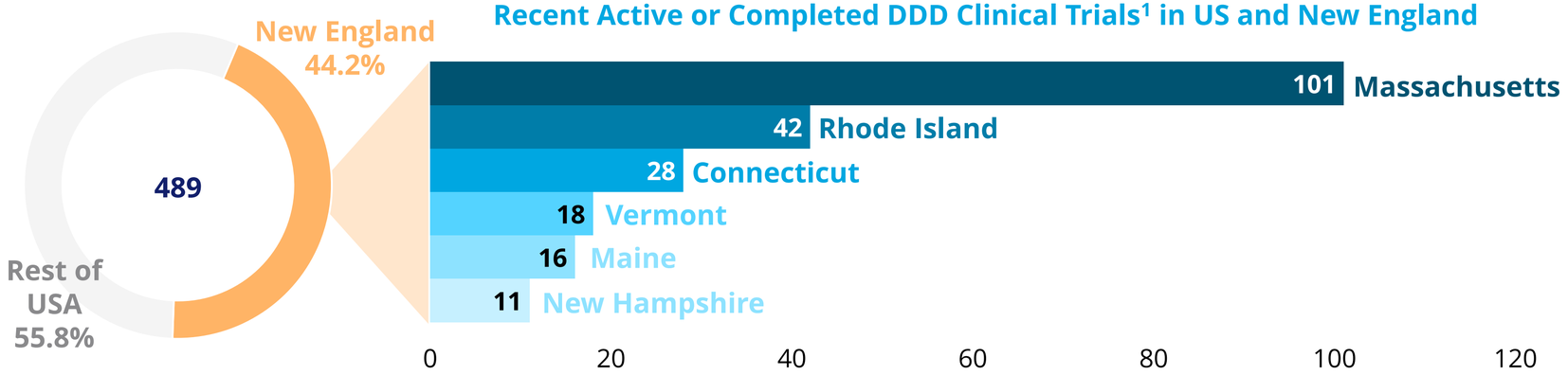
# Clinical Trials in New England

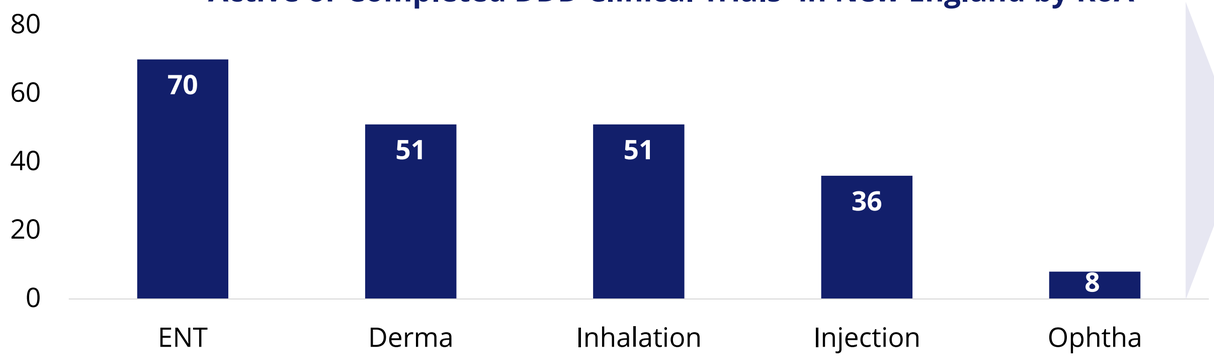
## New England's Global Appeal to Foster Collaboration Between DDD and Pharma

***New England is currently conducting almost half of all DDD clinical trials in the United States, with Massachusetts hosting the majority across all five categories: injection; inhalation; ENT; dermal; and ophthalmology.***

### Key Highlights on DDD Clinical Trials

- Although consisting of only six states, New England has 216 (of 489) total DDD clinical trials, either recently active or completed.
- The ENT market captures most clinical trials in New England with nasal-spray devices as the largest subcategory.
- Massachusetts consistently runs the largest number of clinical trials across all RoA.




**ENT:** Nasal spray, nasal drops

**Injection:** PFS, needle-free injectors, autoinjectors, pen injectors, wearable injectors

**Dermal:** Microneedle patches, transdermal patches

**Inhalation:** pMDI, DPI, nebulizers

**Ophtha:** Eye droppers, eye spray, ocular inserts

Note: [1]Trial starting date between 1/1/2015 and 10/30/2020

Source: clinicaltrials.gov

# Innovative Digital-drug-delivery Devices in New England

## New England's Global Appeal to Foster Collaboration Between DDD and Pharma

***Digital health creates new opportunity for growth and innovative development in the drug-delivery-device industry. Companies throughout New England are pioneers in the space, offering new technologies to improve healthcare.***

### CareTRx®

- The CareTRx® system is made up of a sensor and mobile app that helps patients with asthma or COPD track inhaler use.

GECKO HEALTH INNOVATIONS

**Location:** Cambridge, Massachusetts

Gecko Health Innovations developed a solution for the asthma market with a focus on its sensor for inhalers and smartphone app. Patients can track asthma and COPD medications, symptoms, triggers, peak-flow measurements, and flare-ups.

### Gocap System

- A smart cap that automatically sends drug-delivery data from disposable pen injectors to a mobile app.
- An easy way to monitor compliance and better care.

COMMON SENSING

**Location:** Cambridge, Massachusetts

Common Sensing is working closely with HCPs to help make patient data easy to access and in a way that fits their current lifestyle. Patients can share the data directly with clinicians in real time. This gives physicians the ability to recognize abnormalities that might have previously gone unnoticed.

### EZ-be Pod®[1]

- An innovative wearable device suited for diabetes care and multiple daily injection therapies that is connected to a user-friendly handheld controller in order to store and share patient data.

SG Stevanato Group

**Location:** Boston, Massachusetts

Stevanato Group inaugurated its Technology Excellence Center (TEC) in September 2020 to provide a full-service approach to support biopharma companies along the drug-development journey, from early-phase development to commercialization, including innovative devices.

### Fully Connected Device

- Development of a home-use, Class II treatment device for a client that now includes full connectivity across the device, mobile application, and online. Allows for a clinician portal to view patient progress.

SUNRISE LABS

**Location:** Bedford, New Hampshire

Sunrise Labs has experience in developing medical-device software and electronics. Additionally, it has a portfolio of design work in drug-delivery and other medical devices, making it a strong candidate for clients seeking to develop medical devices in the digital-health space.

Note: [1]EZ-be Pod® is not necessarily developed on the Stevanato Boston site.

Source: CareTRx®, "Introducing accurate, actionable data," 2020; Common Sensing, "Connected Care Designed for Everyone," 2020; Sunrise Labs, "Fully Connected, Next Generation Therapeutic Device," 2020.

# Establishing a Fully Integrated Center in Massachusetts: a Chat With SMC

## New England's Global Appeal to Foster Collaboration Between DDD and Pharma

### Interviewer Profiles

**Chetan N. Patel**
CEO and Owner
***SMC Ltd.***

### Company Profile

**SMC** is a global CDMO for pharmaceutical, diagnostic, and medical devices and an own-IP DDD company which provides end-to-end custom-device services from the initial design to tooling, component manufacturing, assembly, automation, full supply-chain management, and packaging services as well as sterile fill-and-finish capabilities.

**Sales:** ~$500M (2019)

**HQ:** Somerset, WI, US
**Other:** Site in Massachusetts

**Key Highlights in DDD:**

**2021** ▪ Launch of the technology platform Cambridge Pharma to provide capabilities from early-stage processes, including formulation development to manufacturing and complete sterile fill-and-finish capabilities.

**2016** ▪ Acquisition of Oval Medical Technologies Ltd. to acquire early-stage capabilities in the value chain and several autoinjector product platforms.

**Key Delivery Routes**

**Injection** **Inhalation** **Transdermal**

### Insights

**How do you think your customers' needs have evolved in terms of services?**

- One of pharma's main needs today, in the development of new injectable DDDs, is to **accelerate time to market** with **integrated end-to-end technology platforms from formulation development to small- and large-volume fill and finish, including complementary services** such as regulatory testing protocols to know exactly how to customize platforms to customers' drugs and improve device efficiency**.**

**How has SMC adapted to meet these different needs?**

- To begin with, **SMC acquired Oval to increase relevance** for customers through autoinjector- product platforms and upstream capabilities in the value chain.
- SMC has also created a company called **Cambridge Pharma**, which offers **early-stage process development**, including **formulation development, testing, and analytics services** to improve device customization and efficiency, **as well as full sterile fill-and-finish capabilities**.
- SMC is also one of the few companies to **integrate in-house automation** with tooling and injection-molding processes. Thus, SMC has all the capabilities to provide a **complete end-to-end solution under one regulatory umbrella.**

**Why does Massachusetts make sense for you as a key location?**

- For us, Massachusetts is fantastic for several reasons:
  - **Biotechnology** is everywhere: it's a huge driver of new-product development in DDDs.
  - Massachusetts has many excellent high-school and university programs, making **talent acquisition** fantastic.
  - Massachusetts brings a team of very experienced **engineers** and external **design firms**.
  - In Massachusetts, the **distances to supply companies located outside the country are very easy to manage.**

# An Integrated Player Going Upstream and Establishing a Center of Excellence in Massachusetts: a Chat with Stevanato Group

## Interviewer Profiles

**Fabio Bertacchini**
Director of Product Management
***Stevanato Group***

**Steven Kaufman**
Vice President, Drug Delivery Systems
***Stevanato Group***

## Company Profile

**Stevanato Group (SG)** is a global leader in the production of glass primary containers for the pharmaceutical industry and an integrated solution-provider for medical devices, including drug-delivery devices.

**Sales:** 2019 - €573M (~$695M)

**HQ:** Piombino Dese, Italy
**Other:** Site in Massachusetts

**Key Highlights in DDD:**

**2020** ▪ Opening of a **new technology-excellence center in Boston** to support US biopharma's drug-development process along with primary container choice.

**2020** ▪ Partnership with Bexson Biomedical to develop a wearable DDD.

**2019** ▪ Partnership with Duoject Medical Systems to promote the Maverick autoinjector and strengthen the presence of SG in the injection area.

**2017** ▪ License Axis-D IP & technology of Haselmeier to develop a new pen injector, the SG Alina®, supporting the needs of diabetes patients.

**Key Delivery Routes** **Injection** **Inhalation**

## Insights

**How would you describe Stevanato's business model and strategy in the DDD space?**

- Stevanato has **always been involved in the DDD space** as one of the leading suppliers of PFS and cartridges.
- Over the past 5 to 10 years, Stevanato has **sought to develop a broader strategy** by expanding in-house services and capabilities to provide more solutions to customers with a **flexible integrated approach and unique combination of capabilities**.
- **Having full control of the value chain**, from the primary container to the device, through assembly, testing, and other related services, allows customers to **have a single point of contact and accelerate time to market**. This is Stevanato's main differentiating factor.
- Stevanato's strategy in the DDD space is in 3 buckets:
  - **Product management** to ensure that all primary containers work well with devices currently on the market.
  - **Contract manufacturing** of devices for pharma clients, including development support.
  - **Proprietary and licensed devices** in injection and inhalation through key partnerships or acquisitions.

**Why did you choose Boston as the location for your new technology-excellence center and what are the main objectives of this center?**

- In this new technology-excellence center, we will provide **services with added value for clients to advise them in the drug-development cycle**. The key capabilities will initially be on the laboratory side with container closure integrity testing.
- We chose Boston for three main reasons: **proximity to biopharmaceutical companies**, including small and emerging companies; **proximity to device innovation**; and a very **strong talent pool** with knowledge of the DDD industry. It is a central region and therefore a very good match between innovation and geography.

# Section

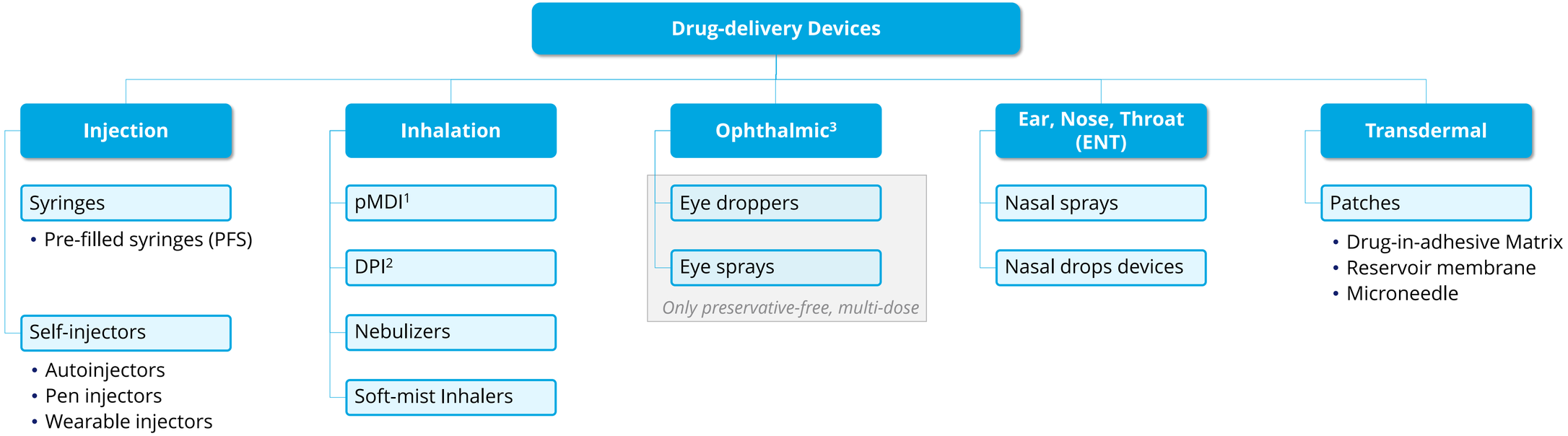
# Drug-delivery-devices Segmentation

## Overview of the DDD Market per Route of Administration

Drug-delivery devices can be segmented into five main groups based on their route of administration (RoA) (i.e., the way in which a drug, fluid, or other substance is taken into the body) and generally classified by the location at which the substance is applied.

*This segmentation* ***includes only products that will be further analyzed in the report.***

### Drug-delivery-devices Segmentation by Route of Administration




Note: [1]pMDI: pressurized Metered-Dose Inhalers; [2]DPI: Dry-powder Inhalers. Source: Javadzadeh, Y. and Yaqoubi, S., "Therapeutic nanostructures for pulmonary drug delivery," 2017; MarketsandMarkets, "Pharmaceutical Drug Delivery Market," 2019; National Institute of Health, Drug Delivery Devices, 2016; Verma, S. *et al.,* "An Overview of Buccal Drug Delivery Device," 2019

# Self-injection[1] DDD market at a Glance

## Overview of the DDD Market per Route of Administration - Injection

***The self-injection DDD market is driven by the innovation on the formulation side with high-viscosity and high-volume drugs, the move toward home care, and the increasing interest of smart-connected devices.***

### Key Players

Own-IP companies and CDMOs have been responsible for developments in auto-injectors and wearable injectors, whereas pharma leads in the pen-injector space, particularly for diabetes

**Own-IP companies / CDMO**

YPSOMED SELFCARE SOLUTIONS

SHL GROUP

West

HASELMEIER Drug Delivery. Tailormade.

BD

flex

Recipharm good for business

JABIL

Nemera

**Pharma**

novo nordisk

### Market Size

**$4.1–4.6B** *Manufacturer price*

### Key Market Trends

- **Wearable injectors,** and to some extent autoinjectors, have become increasingly popular as they enable the **delivery of innovative, high-viscosity, and high-volume drugs** such as biologics.
- **Shifting from in-hospital to at-home self-injection** as a measure to improve patient experience, empower the patient, and reduce healthcare cost.
- There is movement toward **developing smarter and connected self-injectors** to allow for optimized disease management by the patients and physicians and thereby optimize healthcare resources.

**Spotlight**

Medtronic Diabetes has entered the smart insulin-pen market with the acquisition of InPen™.

InPen™ is an insulin self-injector that tracks data through the app and provides personalized dosage recommendations.

> "Everyone is talking about the next technology of wearable devices. The goal is to know how to inject subcutaneously more than 3 ml of drug in 10 to 15 minutes."
>
> *Executive at a global own-IP DDD company*

Note: [1]The self-injection DDD market is composed of needle-free injectors, autoinjectors, pen injectors, and wearable injectors.

Source: Alira Health analysis; Primary interviews; Medical Design Briefs, "Pen and Autoinjectors: Testing for the future," 2019.

# Pre-filled Syringes DDD Market at a Glance

## Overview of the DDD Market per Route of Administration - Injection

***Innovation in pre-filled syringes is found mainly in materials and coating. These developments allow the use of plastic while having similar properties to glass. Moreover, the market will experience a significant rise with COVID-19 vaccines.***

### Key Players

**OWN-IP COMPANIES/CDMOS**

SCHOTT glass made of ideas

NIPRO PHARMAPACKAGING

OWEN MUMFORD Pharmaceutical Services

BD

West

VETTER

GERRESHEIMER

### Market Size

**$1.5–2.0B** *Manufacturer price*

### Key Market Trends

- PFS manufacturers are investing in solutions to **protect patients from needlestick injuries**. But **PFS are highly standardized** and commoditized products with a low level of sophistication, which **limits other innovations**.

- New technologies are mainly focused on the **material of PFS**. For example, recent development in polymers (e.g., cyclic olefin copolymers) have allowed the **shift from glass to plastic syringes** with similar durability, purity, and barrier properties as glass. Moreover, the development of **special coatings** able to block oxygen or other oxidizing gases will improve drug efficacy and product shelf life.

**Spotlight**

The market is expected to witness an exponential increase due to the sudden boost in PFS production to enable COVID-19 vaccines.

> "Syringes have experienced significant growth over the last 20 years. Many drugs are now immediately available in syringes without going through the vial stage."
>
> *Executive at a global own-IP DDD company*

Source: Alira Health analysis; Primary interviews; Lamonte, "How to Inject Mold Cyclic Olefin Copolymers," 2010; Medical Design Briefs, "Pen and Autoinjectors: Testing for the future," 2019; sio2, "Why be limited by glass or plastic?", 2020.

# Innovation in the Injection RoA

## Overview of the DDD Market per Route of Administration - Injection

***Innovations in injection-drug delivery are numerous and mainly concern reusable devices and digital add-on or integrated devices to provide patient monitoring and improve compliance.***

### Innovation in Non-connected Devices

- **Reusable Injectors**: Reusable devices contribute to a lower (waste) footprint, an important consideration in the manufacturing of products, and lowers the cost per injection.

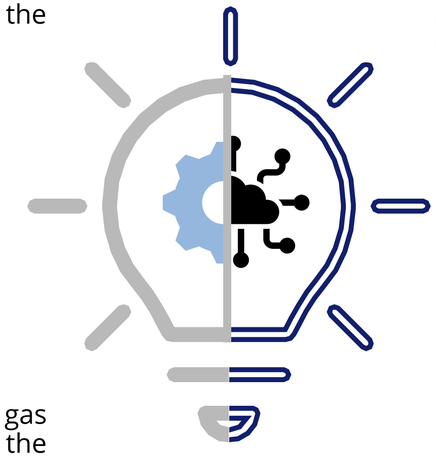
**Example: The Flexi-Q mMU**

The Flexi-Q mMU by E3D is a reusable autoinjector with an activation unit and an easy-to-handle disposable cassette or it can be used with standard pre-filled syringes and vials.

- **Gas-powered Delivery:** Injectors include a novel container of liquefied gas that provides sufficient energy, as pressurized vapor, to power delivery of the drug. The gas-powered system delivers a smooth, consistent delivery profile, vital for patient comfort, increasing adherence and proper dosage.

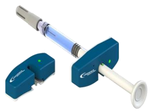
**Example: Syrina® with VapourSoft™ technology**

Syrina® is an autoinjector developed by Bespak in which the driving mechanism is powered by liquified gas, which allows a significantly smaller activation unit than standard autoinjector designs, improving patient ease of use as well as the delivery of more viscous products (e.g., biologics).



### Innovation in Connected Devices and Digital Health

- **Connected Devices**: Connected devices in injection link the DDD to a digital platform to provide the ability to review data for both patients and caretakers in real time.



**Example: Connect™ Auto-sensing Injection System**

The Credence Connect™ incorporates automatic real-time monitoring of critical injection data into a reusable finger grip that enhances the usability of any syringe while measuring and transmitting injection progress in real time.

**Example: OmniPod®**

OmniPod® is a smart and automated wearable injection-drug-delivery platform by Insulet that provides insulin delivery for 3 days. This device improves patient convenience and adherence by providing continuous delivery, reducing the potential for inaccuracy as well as providing data monitoring and reminders through the app.

- **Digital Health:** Digital devices that aid in the actual health care and treatment of the patient.

**Example: InPen™[1]**

InPen™ is a **smart, integrated insulin pen,** used with an app, that helps to ease the daily diabetes insulin administration.

Note: [1]Companion Medical was acquired by Medtronic in August 2020.

Source: Companies' public information

# Inhalation[1] DDD Market at a Glance

## Overview of the DDD Market per Route of Administration - Inhalation

***Future growth in inhalation is expected to rely not mainly on devices, but on innovation in formulations and the use of inhalation to treat non-respiratory conditions. Moreover, inhalation is, along with injection, a very promising RoA for connected devices.***

### Key Players

Own-IP companies and CDMOs have been responsible for developments in pMDI, whereas pharma leads DPI devices.

**OWN-IP COMPANIES / CDMOS**

flex

Aptar pharma

JABIL

Nemera

Recipharm good for business

Kindeva DRUG DELIVERY

**PHARMA**

gsk GlaxoSmithKline

AstraZeneca

### Market Size

**$1.2–1.8B** *Manufacturer price*

### Key Market Trends

- **Most of the innovation related to inhalation is done in formulations** such as changes in propellants. There is **innovation on asthma inhalers' designs to enhance both function and aesthetic**, providing more targeted drug delivery to the lungs and offering more discretion for patients who may feel a social stigma associated with an inhaler's use.
- Despite the rising prevalence of respiratory diseases, there are **no novel drugs for chronic respiratory conditions on the market**, thus limiting the overall market growth. However, new possibilities to treat **other diseases such as CNS or cancer** by inhalation are emerging, in particular with the increase in inhalation doses and the development of drug-formulation development platforms.
- The **smart inhaler segment is expected to show rapid growth** as these inhalers tackle challenges such as the incorrect use of the device, and especially the coordination between actuation and inhalation, causing inhalation of non-consistent doses and/or non-efficient delivery to the site of action.

**Spotlight**

Inhalation is one of the indications with the most development regarding connectivity and digital health, with existing solutions such as Propeller Health *(see next slide)*.

> "The next wave is expected to address higher doses of inhaled drugs to treat conditions other than asthma and COPD. Efforts have been made in the field of insulin, which did not have the success initially expected, but it brings the possibility of treating other diseases such as blood cancer."
>
> *Executive at a global own-IP DDD company*

Note: [1]Inhalation DDD market is composed of pMDI, DPI, nebulizers, and soft-mist inhaler segments.

Source: Alira Health analysis; Primary interviews; Ibrahim, M., Verma, R., and Garcia-Contreras, L., "Inhalation drug delivery devices: technology update," 2015

# Innovation in Inhalation

## Overview of the DDD Market per Route of Administration - Inhalation

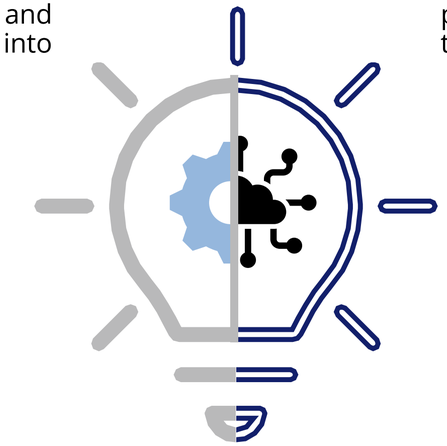
***Inhalation drug-delivery innovations focus on smart inhalers and digital-therapeutics solutions to improve data collection and analysis.***

### Innovation in Non-connected Devices

- **Soft-mist Inhalers (SMIs)**: SMIs are propellant-free inhalers that allow effective delivery. Because the mist contains more particles than MDIs and DPIs and the spray leaves the inhaler more slowly, more of the drug gets into the lungs. However, it is harder to load the dose into the device.

**Example: Ecomyst90**

The Ecomyst90 device is a liquid inhaler using neither propellant nor preservatives. The innovative product is based on spray-nozzle technology from Medspray, which ensures an ultra-fine and precisely dosed spray mist.



### Innovation in Connected Devices and Digital Health

- **Smart Inhalers:** Inhalers with digital features that link to an app to help patients and doctors better manage asthma. Automatically track how often the inhaler is being used to keep records for the patient.

**Example: Connect'Inh**

Connect'Inh is a connected add-on-device adaptable to any type of inhaler with an intuitive application to monitor patients with asthma and improve their compliance. Patients can send a report to their doctors to facilitate their follow-up and management and can share data such as the environmental indicator within a patient community.

- **DTx Inhalation Solutions:** Therapeutic interventions via inhalation devices that are driven by high-quality software programs to prevent, manage, or treat.

**Example: Propeller**

Propeller is a DTx platform for chronic respiratory diseases that combines inhaler add-on sensors, mobile apps, predictive analytics, and personalized feedback to help patients and their physicians better understand and manage respiratory diseases.

Source: Companies' public information; "Digital Therapeutics Alliance, What are digital therapeutics (DTx)?", 2019.

# Ophthalmic[1] DDD Market at a Glance

## Overview of the DDD Market per Route of Administration - Ophthalmic

***The ophthalmic market is driven by preservative-free, multi-dose systems, driving the reusable segment over the disposable one, and the development of smart ophthalmic DDDs.***

### Key Players

**OWN-IP COMPANIES / CDMOS**

Aptar pharma

AERO PUMP

Nemera

Théa
let's open our eyes

### Market Size

**$150–250M** *Manufacturer price*

### Key Market Trends

- Ophthalmic DDD players have developed **preservative-free multi-dose systems for eye drops and sprays**. They are a **cost-effective alternative** for managing the life cycle of preservative-free DDD rather than investing in single-use vials, which is leading to an **increase in multi-dose DDD on the market**.

- There is movement towards **developing smart ophthalmic add-on devices** in order to ensure that the eye drop device and the drop are **well positioned above the eye, detect wrong deliveries and prevent overdosing**, among other features.

> The ophthalmic route is very interesting in 2 ways:
>
> - For regular droppers, the big trend is to move to preservative-free systems and to have the purest formulation possible.
> - Intraocular administration has increased dramatically, it's a very complex route that requires more stringent quality specifications, but the drugs and the diseases are very exciting[2],
>
> *Executive at a Global Own-IP DDD Company*

Note: [1]Ophthalmic DDD market includes eye droppers and eye sprays; [2]Intraocular administration was not included in the scope of this report.

Source: Kumar A, Malviya R and Sharma K, Recent Trends in Ocular Drug Delivery: A Short Review, 2011; Sikandar K, Sharma PK and Visht S, Ocular Drug Delivery Device: an Overview, 2017; Patel PB, Shastri DH, Shelat PK, Shukla AK, Ophthalmic Drug Delivery Device: Challenges and Approaches, 2010; Jervis LP, A Summary of Recent Advances in Ocular Inserts and Implants, 2017; Alira Health analysis; Primary interviews.

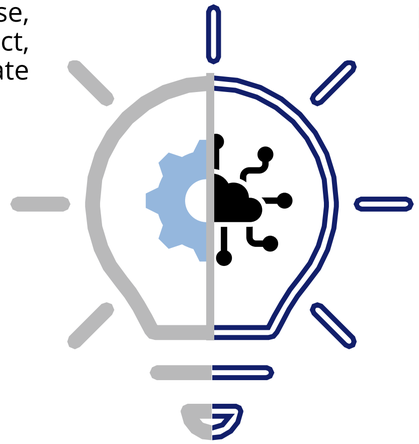
# Innovation in Ophthalmic

## Overview of the DDD Market per Route of Administration - Ophthalmic

***Innovations in ophthalmic drug delivery mainly concern new technologies to develop preservative-free devices and digital innovations to improve patient comfort in administration, monitoring, and compliance.***

### Innovation in Non-connected Devices

- **Preservative-free Systems**: The FDA requires that all multi-dose ophthalmic solutions be preserved against contamination. However, with chronic use, preservatives cause adverse effects, including reduction of the desired effect, allergic response, and toxic reaction. New innovations in device design create multi-use DDDs that do not require the use of harmful preservatives.



**Example: Ophthalmic Squeeze Dispenser (OSD) Technology Platform**

Aptar pharma

Aptar's OSD system does not require preservatives and therefore reduces side effects and ultimately leads to improvement in patient comfort, which increases overall compliance. The mechanical tip-seal technology eliminates the need for preservatives and additives and allows the device to remain sterile for up to 3 months after the first use with a very high microbiological safety.

### Innovation in Connected Devices and Digital Health

- **Digital-health Solutions:** Digital health in ophthalmic DDDs empowers patients/users to better manage and treat their conditions by combining the benefits and features of digital technology into healthcare devices.

**Example: Kali Care Solution**

Kali CARE

Kali Care is a digital-therapeutic ophthalmic solution that includes smart sensors, data analytics, and cloud services to provide digital monitoring across clinical trials. The monitoring system aims at providing a personalized treatment to each patient through real-time data in order to improve adherence. The Kali Care solution provides a reduction in the costs and complexity of ophthalmic clinical trials.

**Example: E-Novelia®**

Nemera

E-Novelia® is a connected reusable add-on-device for eye drops that includes user interface and sensors, among other features, to assist patients in drug administration. This system benefits patients by enhancing instructions for use, usage feedback, and compliance information through the app. This technology is useful for HCPs who can benefit from data analysis and pharma can use data collection to improve their clinical-trial outcomes.

Source: Companies' public information

# Ear, Nose, and Throat (ENT) DDD Market at a Glance[1]

## Overview of the DDD Market per Route of Administration - ENT

***Similar to inhalation, innovation in ENT is driven by the development of drugs to be used outside of local administration for systemic administration. Regarding devices, preservative-free systems are increasingly considered to limit adverse effects.***

### Key Players

**OWN-IP COMPANIES / CDMOS**

Aptar pharma

Recipharm good for business

Nemera

### Market Size

**$400–600M** *Manufacturer price*

### Key Market Trends

- New **ENT devices are being designed and developed** in parallel with drug formulations so that some **currently injected drugs can be administered by the nasal** RoA.
- There is a **strong trend toward unidose DDDs** as drugs are increasingly developed in new therapeutic areas **requiring single delivery**, such as the nasal formulation of naloxone (NARCAN® nasal spray) counteracting the effects of an opioid overdose.
- **Preservatives are used in ENT sprays to maintain sterility**; however, they cause adverse effects in patients. DDD players **have developed multi-dose, preservative-free systems** which have non-vented designs or microfilters to ensure only sterile air passes through.
- The segment of **smart ENT devices is expected to grow rapidly** in the upcoming years, with **electronic locking systems** that count and display the number of actuations and also prevent the devices from being used for a period of time after a predefined number of actuations.

> "The nasal RoA is very interesting because there is a repurposing of drugs. Indeed, the nasal route is still used for local administration (e.g., drugs for cold, allergies, and rhinitis, which are very well-known drugs), but more recently a number of systemic drugs have been developed from the injectable route to the nasal route."
>
> *Executive at a global own-IP DDD company*

Note: [1]ENT DDD market is composed of nasal sprays and nasal-drop devices.

Source: Alira Health analysis; Primary interviews; Ghori, M., Mahdi, M., Smith, A., Conway, B., "Nasal Drug Delivery: An Overview," 2015; Djupesland, P., Nasal Delivery Method, 2012

# Innovation in ENT

## Overview of the DDD Market per Route of Administration - ENT

***The ENT market is driven by the development of preservative-free systems and emerging research in nasal vaccine delivery. Innovations in digital health are centered around advances in electronic nasal sprays.***

### Innovation in Non-connected Devices

- **Preservative-free nasal delivery systems:** Nasal sprays typically contain preservatives to keep the devices sterile but can have negative side effects in patients. DDD players have developed preservative-free systems which have non- vented designs or microfilters to ensure only sterile air passes through. For example, Nemera has developed Advancia® PF to deliver preservative-free nasal- spray drugs to patients.

**Example: Advancia®** Nemera

Preservative-free nasal spray that has a user-independent feature for full-dose delivery. High-performing pump with excellent dose consistency and prime retention.

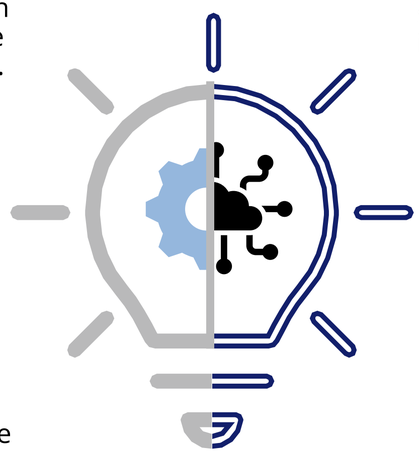
- **Nasal Vaccine Delivery:** Nasal vaccine delivery is a simple and cost-effective method of vaccination with enhanced patient compliance. Research is underway to explore the nasal vaccine-delivery systems, especially with the outbreak of COVID-19. Products like FluMist® already exist for the standard flu vaccine.

**Example: CoroFlu**

WISCONSIN UNIVERSITY OF WISCONSIN–MADISON

CoroFlu, a vaccine against COVID-19 through the nasal drug-delivery route, is currently under development as a joint collaboration with the University of Wisconsin–Madison, FluGen, Inc., and Bharat Biotech.

FluGen BHARAT BIOTECH



### Innovation in Connected Devices and Digital Health

- **Electronic Nasal Sprays:** Several nasal DDD players are developing electronic smart nasal drug-delivery solutions to assist with patient compliance and integrate with existing cloud solutions.

**Example: e-Lockout** Aptar pharma

The e-Lockout is an integrated electronic nasal lockout device that features a lockout mechanism, limiting the number of doses available within a 24-hour period. As such, patients can use the device only at specified intervals.

**Example: Safe'n'Spray™** Nemera

Safe'n'Spray™ is the integrated device with a reusable electronic locking unit and fingerprint identification used
to monitor drug delivery and prevent overdosing. The Safe'n'Spray™ pairs with the eNemera cloud solution to store and share data.

Source: Companies' public information; Ramivikas, M. *et al.,* "Nasal Vaccine Delivery," 2016

# Transdermal DDD Market at a Glance[1]

## Overview of the DDD Market per Route of Administration - Transdermal

***The transdermal market is driven by the development of microneedle patches which allow a systemic drug delivery and represent an easier way to deliver the medicine with patients able to self-administer the drugs.***

### Key Players

**OWN-IP COMPANIES / CDMOS**

LTS TRANSDERMAL. MARKETLEADER.

Kindeva DRUG DELIVERY

### Market Size

**$300–500M** *Manufacturer price*

### Key Market Trends

- Over the last few years, the market has **witnessed technological advancements** in the patch system, including precise and controlled drug delivery by **microneedles,** which lead the drug directly to the epidermis or upper dermis region, from where the drug can go directly into systemic circulation, and which have bolstered market growth.

- In addition, **the segment of transdermal electronic devices** and smart wearable technologies including transdermal sensors **is expected to grow** in the upcoming years with monitoring of physiologic parameters (i.e., insulin blood level) in order **to precisely deliver a personalized dose of drug in real time.**

> "We are working on some novel technologies within transdermal, applying human-centered design principles in the product development to make it easier for people to use gel patches or other complex formulations…. The microneedle market is predicted to grow very rapidly."
>
> *Executive at a global CDMO*

Note: [1]The transdermal DDD market is composed of patches, including drug-in-adhesive matrix, reservoir membrane, and microneedles.

Source: Alira Health Analysis; Primary interviews; The Pharma Journal, "Recent Trends in Challenges and Opportunities in Transdermal Drug Delivery Device," 2012; NCBI, "Topical and Transdermal Drug Delivery: From Simple Potions to Smart Technologies," 2019

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# Innovation in Transdermal

## Overview of the DDD Market per Route of Administration - Transdermal

***Innovations in transdermal include skin ablation and microneedles with iontophoresis, bringing transdermal drug-delivery devices into the digital-health space.***

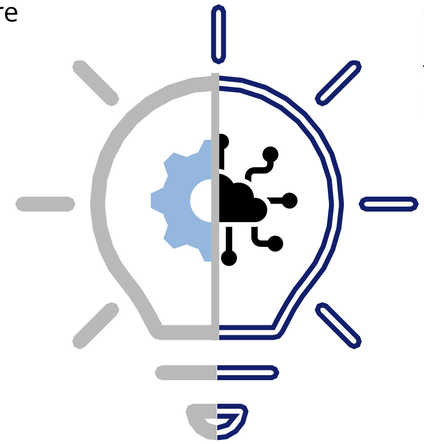
### Innovation in Non-connected Devices

- **Hollow Microneedles:** Advances in microneedle research have led to the development of hollow microneedles, which can deliver higher doses and are engineered for drug release.

**Example: Hollow Microstructured Transdermal System (hMTS)**

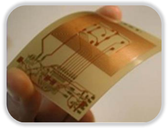
Kindeva DRUG DELIVERY

hMTS is a new intradermal delivery system and a new way to deliver vaccines with a patient-friendly design.



### Innovation in Connected Devices and Digital Health

- **Smart Patches:** Smart patches allow physicians to administer and control the dosage of medicinal products delivered to the patient. This allows for increased efficacy, improved bioavailability, and minimized side effects. The transdermal patch also prevents doses being missed or taken incorrectly by patients requiring third-party assistance.



**Example: RHEPatch**

Rhenovia Pharma

RHEPatch is a transdermal patch allowing the controlled administration of drugs. 1-7 different molecules can be administered in quantities adapted to the patient's needs, thanks to an on-board electronic system programmed by the attending physician.

- **Intelligent Iontophoresis:** Flexible iontophoresis patch that is self-powered and microprocessor-controlled.

**Example: ActivaPatch®**

North Coast MEDICAL & REHABILITATION PRODUCTS

An intelligent biofeedback microprocessor and SmartPower LED allow the patch to communicate with both clinician and patient to guarantee effective drug delivery.

Source: Companies' public information; Alliance of Advanced BioMedical Engineering, "Innovations in Transdermal Drug Delivery," 2018; Bairya, S., *et al.*, "Microneedles: an emerging transdermal drug delivery device," 2011

# Section

# The FDA's Guidelines on Medical Devices

## Overview of the Regulatory Landscape

***The FDA has a very specific definition of medical devices with three distinct classes based on level of risk, each with their own set of regulations and requirements for market approval. Drug-delivery devices fall into either Class 1 or Class 2.***

### Medical Devices

**Definition:** A product that is labeled or used in one or more of the following ways:

1. An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory
2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals
3. Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purpose through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes

### Differences in FDA Medical-device Classes

**Low-risk**
Class 1: General Controls

Not intended for use in supporting or sustaining life or of substantial importance in preventing impairment to human health, and they may not present a potential unreasonable risk of illness or injury

**Class 1 Examples:** Tongue depressor, oxygen mask, bandages

**Moderate-risk**
Class 2: General Controls & Special Controls

Devices for which general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device

**Class 2 Examples:** Syringes, contact lenses, surgical gloves, blood-transfusion kits

**High-risk**
Class 3: General Controls & Pre-market Approval

Devices for which general controls are insufficient to provide reasonable assurance of their safety and effectiveness

**Class 3 Examples:** Pacemakers, defibrillators, implanted prosthetics, breast implants, cochlear implants

Drug-delivery devices are medical devices that typically fall into **Class 2** because they do not support life or present an unreasonable risk of illness or injury. However, because most DDDs are paired with drugs or biological products, **they result in a new classification: combination products.**

Source: FDA, Medical Device Overview, 2018; FDA, Overview of Device Regulation, 2020; Fenton, R., "What Are the Differences in the FDA Medical Device Classes?", 2019.

# The FDA's Guidelines on Combination Products

## Overview of the Regulatory Landscape

***The FDA defines combination products as products that combine drugs, devices, and/or biological products. The FDA outlines four main ways to determine what is a combination product.***

### Combination Products

**Definition:** The FDA defines combination products as products composed of at least 2 different components of drugs, biological products, and a device. Under 21 CFR 3.2 (e), a combination product includes:

1. A product comprised of two or more **regulated components physically, chemically, or otherwise combined** or mixed and produced as a single entity.
2. Two or more **separate products packaged together** in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products.
3. A drug, device, or biological product packaged separately that is **intended for use only with an approved individually specified drug, device, or biological product.**
4. Any **investigational drug, device, or biological product** packaged separately that is for use only with another individually specified investigational drug, device, or biological product.

### What qualifies as a combination product?

**Drug/Biologic**

**Drugs** are substances recognized by an official pharmacopoeia or formulary, substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Substances (other than food) intended to affect the structure or any function of the body.
**Biologics** can be composed of sugars, proteins, nucleic acids, or complex combinations of these substances, or may be living entities such as cells and tissues.

+

**Drug-delivery Device**

**Drug-delivery devices** are Class 1 or Class 2 medical devices made up of engineered technologies for the targeted delivery and/or controlled release of therapeutic agents.

=

**Combination Product**

**Combination products** are therapeutic and diagnostic products that combine drugs and/or biologics with medical devices.

- Examples of traditional drug/device combination products include pre-filled syringes (e.g., insulin autoinjectors), drug-coated devices (e.g., drug-eluting coronary stents), and co-packages (e.g., a first-aid kit containing antibacterial ointment)

Source: FDA, Drugs@FDA Glossary of Terms, 2017; FDA, Combination Products, 2020; Alira Health analysis

# The FDA's Regulation Pathway – Drug-delivery Device

## Overview of the Regulatory Landscape

***The FDA Office of Combination Products helps classify combination products to move forward for approval. Master files help ease the product-approval process for combination productions because they can be authorized by DDD companies for multiple applicants.***

### Drug-delivery-device Regulation Pathway


**FDA's Office of Combination Products (OCP)**

- The primary role of the OCP is to classify medical products as drugs, devices, biological products, or combination products and assign them to an FDA center for pre-market review and regulation. The products are assigned to an FDA center based on the Primary Mode of Action.

The device information **may be included in the submissions** or **provided in a device master file.**

**Master Files**

- Master files (MFs) are voluntary submissions of information to the FDA that may be used to provide confidential, detailed information to the FDA about the facilities, processes, or articles used in the manufacture, processing, packaging, or storing of one or more regulated products.
- The person holding the MF may authorize one or more sponsors or applicants to reference information contained in the MF to support a submission to the FDA without having to disclose that information to the sponsors or applicants.

Notes: [1]Center for Drug Evaluation and Research; [2]Center for Devices and Radiological Health; [3]Center for Biologics Evaluation and Research

Source: FDA, Master Files, 2017; FDA, "Master Files for CBER-Regulated Products 2020"; Paladin Medical, Device Master File (MAF), 2015; Alira Health analysis

# Europe's Guidelines on Medical Devices

## Overview of the Regulatory Landscape

***The MDR has a very specific definition of medical devices with four distinct classes based on level of risk, each with its own set of regulations and requirements for market approval.***

### MDR - Medical Devices

**Definition:** The MDR defines medical devices as products or equipment that are intended for medical use, but must not exert a pharmacological, immunologic, or metabolic action.

- √ Medical devices in the EU must undergo a conformity assessment to demonstrate that they meet legal requirements ensuring that they are safe and perform as intended.
- √ The conformity assessment usually involves an audit of the manufacturer's quality-management system and a review of technical documentation from the manufacturer on the safety and performance of the device.
- √ Manufacturers should place a CE (Conformité Européenne) mark on a medical device once the NB has issued the certificate.

! The MDR was to have come into effect by May 2020, but the new **Date of Application has been extended to May 2021** due to the impact of COVID-19.

A new group called the **Medical Device Coordination Group** has been implemented to help coordinate efforts between member states and assist with new changes to the medical-device legislation.

Source: Medical Devices Regulation (MDR), 2017

### Differences in Medical-device classes

| | |
|---|---|
| **Low-risk** Class I | Present a low potential risk such as reusable surgical instruments, non-invasive medical devices, or certain temporary-use medical devices. **Examples:** Oxygen mask, bandage, eyeglasses, wheelchair |
| **Medium-risk** Class IIa | Present a medium potential risk such as reusable surgical instruments and for temporary-use invasive medical devices. **Examples:** Catheter, contact lenses, surgical gloves |
| **High-risk** Class IIb | Present a high potential risk such as long-term implantable medical devices. **Examples:** Infusion pump, hemodialyzer, internal sutures |
| **Critical-risk** Class III | Present a critical potential risk such as long-term implantable medical devices in contact with vital organs (i.e., heart, central circulatory system, or central nervous system, etc) or implants (i.e., breast, knee, etc) **Examples:** Pacemaker, breast implant, defibrillator |

**Drug Delivery Devices (DDD) classification**

Because most DDDs are paired with chemical/biologics medicinal products, they are regulated as combination products. Different aspects should be considered when classifying combination products (see next slide).

### Notified Bodies

√ **Notified Bodies (NBs)** are public or private organizations designated by the National Competent Authorities (NCA) of the EU member states. NBs perform the conformity assessment procedures and issue the medical-device certificates.

√ Not all NBs are able to evaluate all types of medical devices. The manufacturer of the MD has to select the NB that includes their medical device within the scope of their services. The list of NBs is available at NANDO database.

! With the MDR coming soon, NBs are expected to have a huge increase in their workload in the following years. Thus, **NB availability should be considered by the manufacturer** to ensure that its medical device will be certified within the expected timeline.

# Europe's Regulation Pathway for Combination Products

## Overview of the Regulatory Landscape

***Different regulatory pathways apply, depending on how the combination of a medicinal substance and a medical device is envisaged.***

### Combination Products Regulatory Framework

**Combination Products in EU**

- Medicinal substances used in combination with a medical device, including also when they enable the **delivery of medicine**.
- The **MDR** and the **EMA Quality Guideline for Combination Products**[1] do not use exactly the same terms for combination products classification.

**Devices incorporating a medicinal substance as an integral part:** The medicinal product is an integral part of the device (**MDR Article 1(8)**).

- **If the medicinal substance is exerting the primary mode of action:** The whole product is regulated as a **medicine,** but the opinion of a NB is needed.

  *Examples:* Pre-filled syringes and pens, patches for transdermal drug delivery, and pre-filled inhalers.

- **If the medicinal substance is exerting an ancillary action:** The whole product is regulated as a **medical device**, but the scientific opinion from the EMA or NCA is needed.

  *Examples:* Heparin-coated stent, wound-dressing with antibiotic.

**Devices intended to administer a medicinal product:** The medicinal product is administered via a medical device (**MDR Article 1(9)**).

- **Single integral non-reusable product:** The medicinal product and the device form a **single integral product** exclusively for use in the combination. It is regulated as a **medicine**, but the opinion of a NB is needed.

  *Examples:* Pre-filled syringes and pens, patches for transdermal drug delivery, and pre-filled inhalers.

- **Co-packaged:** The medicinal product and the device are **separate items contained in the same pack**. They each follow their own regulatory pathway.

  *Examples:* Reusable pen for insulin cartridges; tablet delivery system with controller for pain management.

- **Cross-labeled:** The medicinal product and the device are **separate items not contained in the same pack**. They each follow their own regulatory pathway.

  *Examples:* Inhalation drug to be used with a specific inhaler; pen for insulin cartridges that are sold separately.

**Drug Delivery Device (DDD)** (see next slide)

Note: [1]EMA "Guideline on the quality requirements for drug-device combinations," Draft, May 2019, EMA/CHMP/QWP/BWP/259165/2019

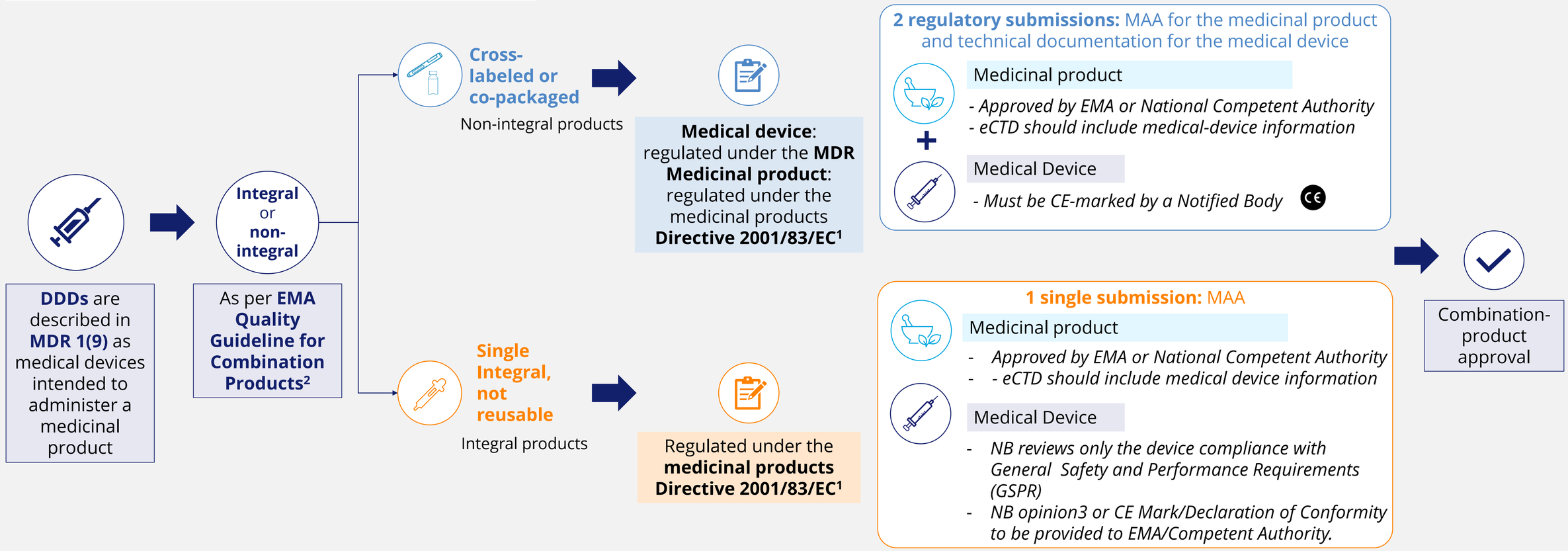
Source: EMA

# Europe's Regulation Pathway – Drug Delivery Device

## Overview of the Regulatory Landscape

***The MDR classifies a medical device intended to administer a medicinal product as a combination product under Article 1(9). There are two main categories of DDDs: integral and non-integral. Different regulations apply to these two categories.***

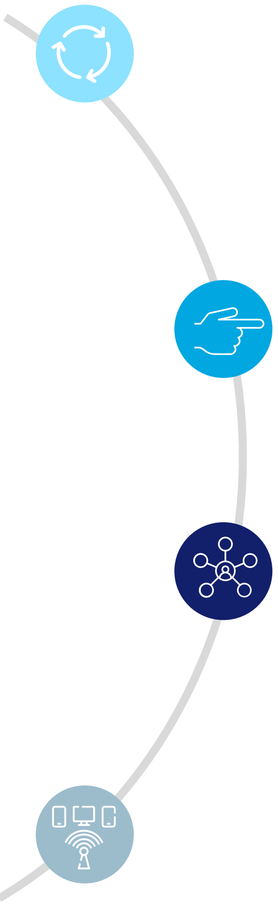
### DDD Regulatory Pathway - Europe




Note: [1]Directive 2001/83/EC of the European Parliament and the Council of 6, November 2001 on the Community code relating to medicinal products for human use; [2]EMA Guideline on the quality requirements for drug-device combinations, Draft, May 2019, EMA/CHMP/QWP/BWP/259165/2019; [3]NB opinion is required for Class III, IIa IIb devices. No NB opinion for Class 1 except for Class I sterile/measuring medical devices. Source: Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)

# Section

# Conclusion



The DDD and medical-device industry has an opportunity to **enhance the patient experience and drive better outcomes** through increased adoption of **patient-centric approaches**. By giving patients a voice throughout the development life cycle and pairing those insights with a solid understanding of all stakeholders in the healthcare ecosystem, the industry can broaden its scope from enabling the proper usage of a device to generating evidence of the device's positive impact.

Industry participants are **developing their service offerings, integrating their value chains, and adding capabilities outside of their historical core business** to become early-stage partners and provide increasing value to their customers.

The **Internet of Medical Things** (IoMT) certainly **opens new opportunities for industry players** to take an important role in pharma's digital-health monetization strategies and patient outcomes. **Business models still have to be found and could start with DDS players co-developing digital-health ecosystems with pharma at very early stages** of drug development or repositioning processes (rather than developing connected devices alone). Both DDS and pharma, particularly midsized pharma without digital-health teams, believe **partnering would enable the sharing of financial risks** and **building knowledge** while engaging with more patients, payors, HCPs, and other key stakeholders currently engaged at later stages.

Concretely, for both connected solutions and traditional mechanical devices, we believe **patients need to be engaged far beyond traditional human-factor engineering and be part of the ecosystems' development** to guarantee the relevance of the solution to them, maintain adherence, and demonstrate outcome.

The **goal is no longer to enable the proper delivery of a molecule**, but to assist pharma in **generating evidence of the treatment's positive impact** and to **secure the patients' needs are at the center** of the development process.

Source: Alira Health analysis

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**Aude Ouensanga** is a Partner at Alira Health, where she leads the Drug Delivery Systems practice. She supports clients including platform developers, design firms, CDMOs, pharmas, and MedTechs. After starting her career in France, she has been based in Boston since 2015. Aude oversees market-opportunity assessments, commercial due diligences, corporate strategies, digital-health strategies, and M&A in the US, Europe, and APAC. She manages and serves on the boards of several Alira Health Ventures companies. Before joining Alira Health in 2012, Aude worked as a strategy analyst at Novartis Pharma and as a M&A analyst at BNP Paribas. She graduated from France's Emlyon Business School.

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**Laure Girard** joined Alira Health in 2018 and has since been working in strategy consulting for a variety of healthcare verticals, mainly Drug-delivery Devices and Medical Devices Contract Manufacturing. Previously, she worked at General Electric Healthcare, where she was in charge of logistics in the MRI devices business. Laure holds a master's degree in Business Management from EDHEC Business School in France.

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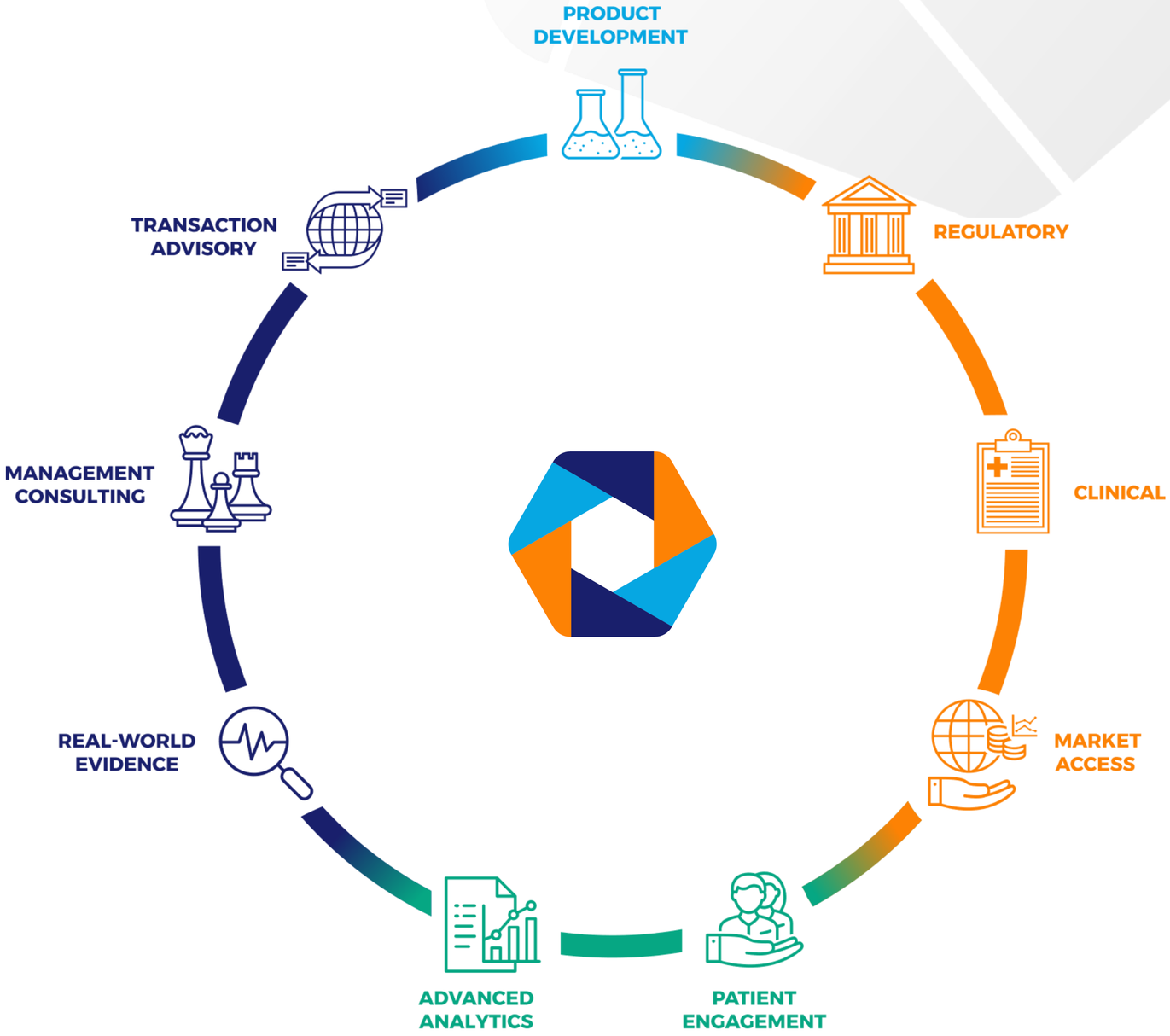
**Marie Vaillant** joined Alira Health's Paris office in August 2020 as an analyst in Strategy and M&A transactions. She has a double academic background in engineering and management. Marie holds a master's degree in Management from Emlyon Business School and has a background in biomedical engineering from MINES Saint-Etienne. With prior experiences as a consultant and engineering assistant in a medical-device company, Marie has acquired knowledge in the field of healthcare and life sciences. Since joining Alira Health, Marie has worked on several strategy-consulting projects, including business- opportunity assessments for CDMOs and med tech companies.

# About Alira Health

## A Life-cycle Approach

***We provide a variety of services under the same umbrella and with a holistic approach and clear vision: to offer unparalleled support and value at every stage of your corporate and product evolution.***



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